The Translational Research Acceleration Initiative

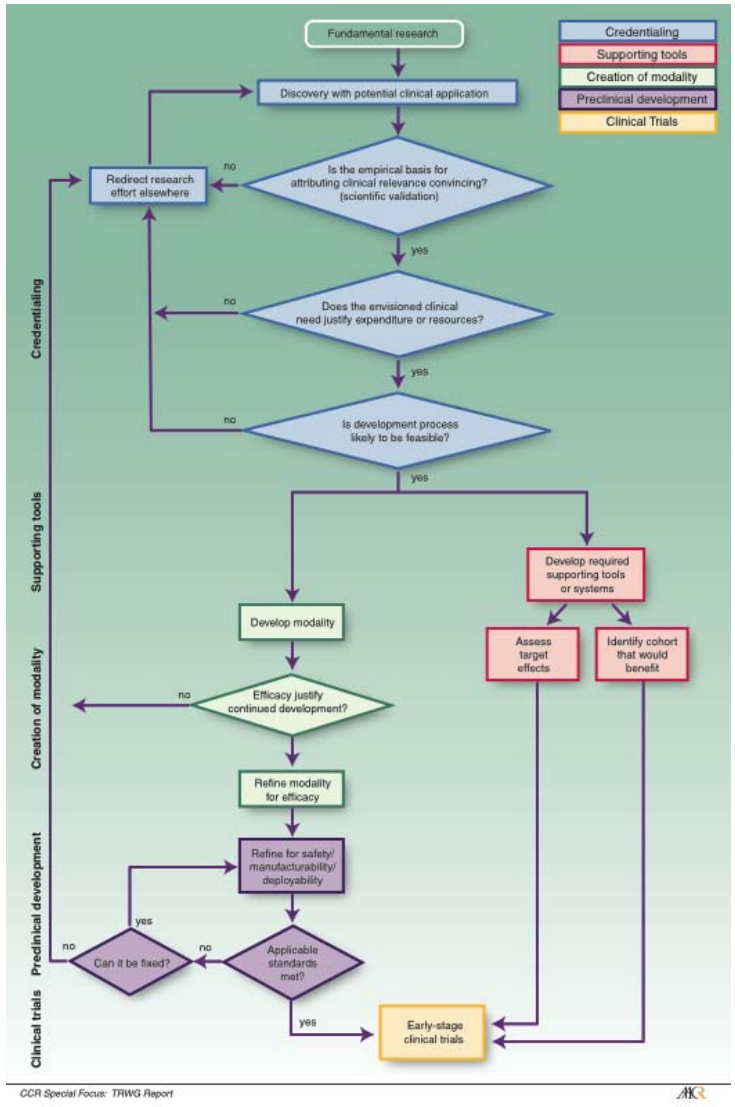
Clinical Trials and Translational Research Advisory Committee

November 4, 2009

Lynn M. Matrisian

Special Assistant, NCI

TRWG: The Challenge of Early Translation



How can we best assure that:

- The most promising concepts enter the developmental pathways?
- Concepts that do enter advance to the clinic or to productive failure?
- Progress is as rapid, efficient and effective as possible?

15 TRWG Initiatives with Implementation Plans

Optimize and enhance NCI functions that are critical for translational research

- **Coordinated Management**
  - Integrated NCI management
  - Budget designation
  - TR coding
  - Prioritization process
- **Tailored Funding**
  - Modify TR award mechanisms
  - Improve investigator-initiated TR awards
  - STRAP awards
  - Academic/industrial collaborations
- **Operational Effectiveness**
  - Project management
  - Core services coordination
  - Enhance biorepositories
  - Improve IP negotiations
  - Enhance foundation/advocate group collaborations
  - Enhance training/incentives

Develop a new process to accelerate translational cancer research

www.cancer.gov/trwg

Translational Research Acceleration Initiative

Select several projects/year that are "ripe" for translation

- Translational Research Acceleration Process DOES:
  - Gather information on translational opportunities
  - Prioritize translational research opportunities
  - Develop a funding & project management plan to accelerate prioritized opportunities
- Translational Research Acceleration Process DOES NOT:
  - Impact Discovery research
  - Replace existing infrastructure or mechanisms for clinical or translational research

Process to Accelerate Translational Science Initiative

NCI's Clinical Trials and Translational Research Advisory Committee (CTAC) recommended that NCI proceed with establishing a process to accelerate translational cancer research (Dec 08):

Gather information

↓

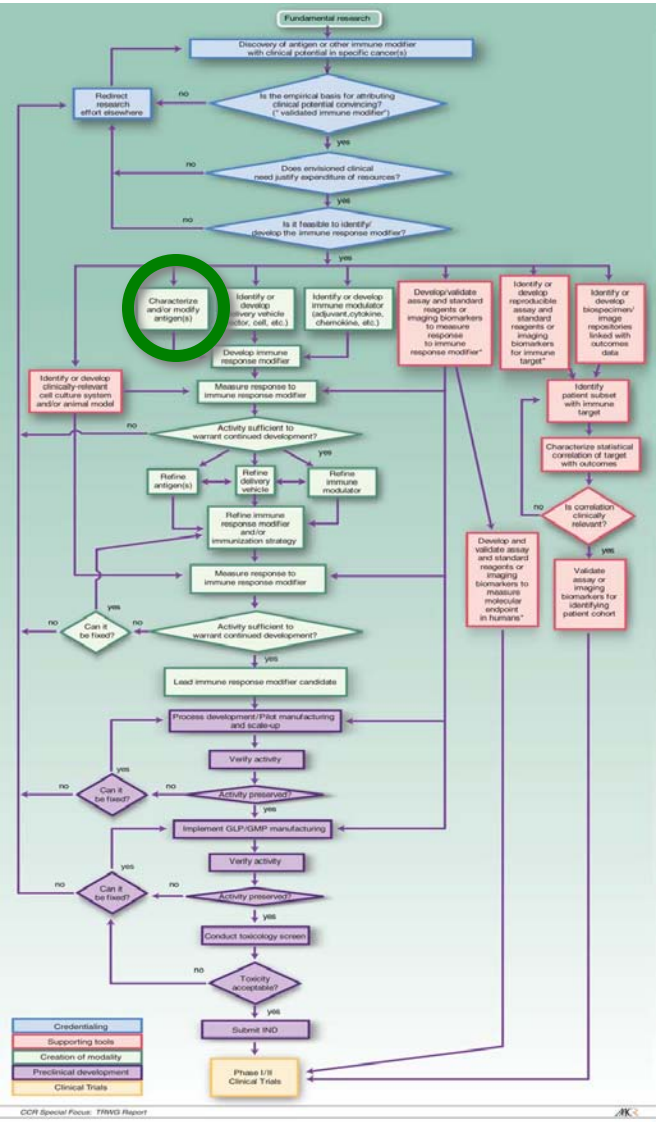
Prioritize

↓

Fund & Manage

Immune Response Modifier Pathway Pilot Project

Pilot Project: Immune Response Modifier Pathway

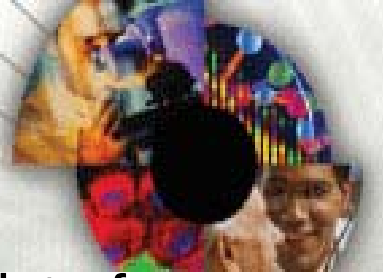


- Piloted information gathering and prioritization with Immune Response Modifier Pathway
  - Most complex of the Pathways
  - Previous prioritization of Immune Response Modifiers (summer 2007)

    http://dcb.nci.nih.gov/ImmunAgentWork
  - A group of committed immunologists/immunotherapists could be identified *(Mac Cheever, Fred Hutchinson Cancer Center)*
- Phase I: Focused on Antigen development
- Phase II: Expanded to entire IRM Pathway

Immune Response Modifier Pilot Prioritization Process

Project: Antigens (Phase I)



- Purpose: To develop a well-vetted ranked priority list of cancer vaccine target antigens based on pre-defined and pre-weighted objective criteria
- Process
  - Developed list of “ideal” cancer antigen criteria/characteristics
    - Email
    - 36 experts
  - Prioritized and weighted criteria using pair-wise comparisons
    - Web-based, Sept 2008
    - 20 experts
  - Selected 100 representative antigens
  - Assembled information on pre-defined criteria from experts for each antigen
    - ~79 experts, final 75 antigens
  - Ranked antigens based on the pre-defined pre-weighted criteria
    - Face-to-face, Oct 2008
    - 16 reviewers

Clin Can Res, 15: 5323, 2009

Immune Response Modifier Pilot Prioritization Process

Project: IRM PATHWAY (Phase II)

The IRM Subgroup of the Process to Accelerate Translational Science (PATS) Working Group of CTAC

- Purpose: To pilot the prioritization of IRM Pathway Translational Research Opportunities using pre-defined and pre-weighted objective criteria

- Process
  - Developed list of “ideal” criteria/characteristics for IRM Pathway Translational Research Opportunities based on the IRM Pathway and the previous Antigen Prioritization experience
  - Prioritized and weighted criteria using pair-wise comparisons
    - Web-based pilot prioritization (4 extramural investigators)
    - Face-to-Face meeting April 19, 2009 at AACR (21 investigators)
    - Subsequent facilitated or asynchronous web sessions (15-21 votes/category)

IRM Subgroup of the PATS Working Group members:

Co-Chairs

Martin A. Cheever, *Fred Hutchinson*
Lynn Matrisian, *NCI*

James Allison, *Mem. Sloan-Kettering*
Lisa Butterfield, *Univ. of Pittsburgh*
Nora Disis, *Univ. of Washington*
Olivera Finn, *Univ. of Pittsburgh*
Bernie Fox, *Providence CC*
Dmitry Gabrilovich, *Moffitt CC*
Thomas Gajewski, *Univ. Chicago*
Toby T. Hecht, *NCI*
Elizabeth Jaffee, *John Hopkins*
Francesco Marincola, *NIH*
Svetomir Markovic, *Mayo*
Ira Mellman, *Genentech*
Karolina Palucka, *Baylor*
David Peace, *Univ. Illinois*
Nickolas Restifo, *NCI*
Jeffrey Schlom, *NCI*
Howard Streicher, *NCI*
Mario Sznol, *Yale Univ*
Walter Urba, *Providence CC*
Jeffrey Weber, *Moffitt CC*
Louis Weiner, *Georgetown*
Jedd Wolchok, *Mem. Sloan-Kettering*

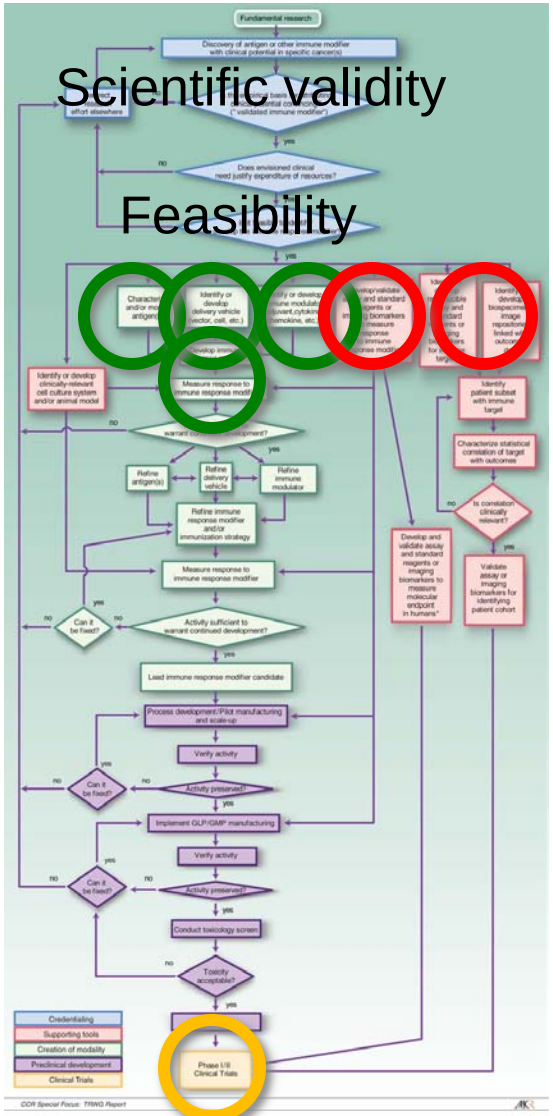
Prioritization Tool

Analytical Hierarchy Process (AHP):
A structured technique for complex decision making

- Based on mathematics and human psychology
- Provides a comprehensive framework
  - To structure the problem
  - To represent and quantify key elements
  - To relate those elements to overall goals
  - To evaluate alternative solutions

Saaty, T.L., 1970's

IRM Pathway Criteria and Subcriteria
(IRM SG of PATS WG)



Pathway Components:

- Target (Antigen/Antibody/T-cell)
- Formulation (cell preparation, delivery vehicle, adjuvant, etc)
- Immune Modifier Agent (cytokines, etc)
- Combination Regimen
- Assay for Immune Response
- Assay to select patient population
- Availability of Patients for Trials

Scientific Validity & Feasibility for each component

Rating scales/level of evidence for each criteria

Pre-determined, weighted criteria for IRM prioritization

CRITERIA Subcriteria	RATING SCALE	LEVEL OF EVIDENCE in descending order
IMMUNE MODIFIER AGENT (cytokines, etc)		
Scientific validity	Augments specific immunity in human trials	Data for augmenting specific immunity in human trials is superb as judged by an informed expert
		Data for augmenting specific immunity in human trials is adequate
	Augments specific immunity in animals	Data for augmenting specific immunity in animals is superb as judged by an informed expert
		Data for augmenting specific immunity in animals is adequate
	Augments specific immunity in vitro	Adequate data for augmenting specific immunity in human cells in vitro
	No in vitro or in vivo data available	No in vitro or in vivo data available
Feasibility	Manufacturing of clinical grade agent	GMP/clinical grade manufacturing of the agent at scale is reproducible and reliable
		Scalable clinical grade manufacturing process for the agent has been piloted
	Manufacturing of clinical grade class-related modifier	Scalable clinical grade manufacturing process for the agent class has been demonstrated
	Available as a laboratory grade product	Laboratory product only
	Not developed	Not completely developed

Process to Accelerate Translational Science Initiative

Gather information

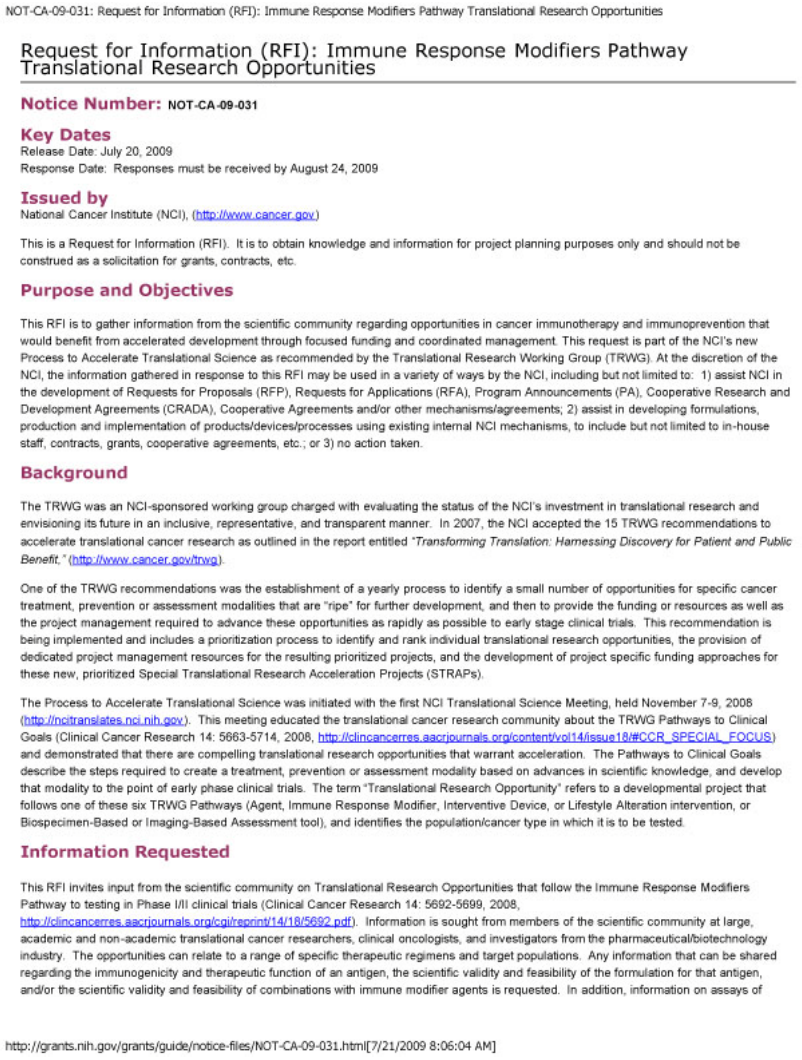
Prioritize

Fund & Manage

Gather IRM Translational Research Opportunities

Request for Information for IRM Translational Research Opportunities July 20-Aug 24, 2009

40 submissions



NOT-CA-09-031: Request for Information (RFI): Immune Response Modifiers Pathway Translational Research Opportunities

Request for Information (RFI): Immune Response Modifiers Pathway Translational Research Opportunities

Notice Number: NOT-CA-09-031

Key Dates
Release Date: July 20, 2009
Response Date: Responses must be received by August 24, 2009

Issued by
National Cancer Institute (NCI), (http://www.cancer.gov)

This is a Request for Information (RFI). It is to obtain knowledge and information for project planning purposes only and should not be construed as a solicitation for grants, contracts, etc.

Purpose and Objectives

This RFI is to gather information from the scientific community regarding opportunities in cancer immunotherapy and immunoprevention that would benefit from accelerated development through focused funding and coordinated management. This request is part of the NCI's new Process to Accelerate Translational Science as recommended by the Translational Research Working Group (TRWG). At the discretion of the NCI, the information gathered in response to this RFI may be used in a variety of ways by the NCI, including but not limited to: 1) assist NCI in the development of Requests for Proposals (RFP), Requests for Applications (RFA), Program Announcements (PA), Cooperative Research and Development Agreements (CRADA), Cooperative Agreements and/or other mechanisms/agreements; 2) assist in developing formulations, production and implementation of products/devices/processes using existing internal NCI mechanisms, to include but not limited to in-house staff, contracts, grants, cooperative agreements, etc.; or 3) no action taken.

Background

The TRWG was an NCI-sponsored working group charged with evaluating the status of the NCI's investment in translational research and envisioning its future in an inclusive, representative, and transparent manner. In 2007, the NCI accepted the 15 TRWG recommendations to accelerate translational cancer research as outlined in the report entitled "*Transforming Translation: Harnessing Discovery for Patient and Public Benefit,*" (http://www.cancer.gov/trwg).

One of the TRWG recommendations was the establishment of a yearly process to identify a small number of opportunities for specific cancer treatment, prevention or assessment modalities that are "ripe" for further development, and then to provide the funding or resources as well as the project management required to advance these opportunities as rapidly as possible to early stage clinical trials. This recommendation is being implemented and includes a prioritization process to identify and rank individual translational research opportunities, the provision of dedicated project management resources for the resulting prioritized projects, and the development of project specific funding approaches for these new, prioritized Special Translational Research Acceleration Projects (STRAPs).

The Process to Accelerate Translational Science was initiated with the first NCI Translational Science Meeting, held November 7-9, 2008 (http://ncitranslates.nci.nih.gov). This meeting educated the translational cancer research community about the TRWG Pathways to Clinical Goals (Clinical Cancer Research 14: 5663-5714, 2008, http://clincancerres.aacrjournals.org/content/vol14/issue18/#CCR_SPECIAL_FOCUS) and demonstrated that there are compelling translational research opportunities that warrant acceleration. The Pathways to Clinical Goals describe the steps required to create a treatment, prevention or assessment modality based on advances in scientific knowledge, and develop that modality to the point of early phase clinical trials. The term "Translational Research Opportunity" refers to a developmental project that follows one of these six TRWG Pathways (Agent, Immune Response Modifier, Interventive Device, or Lifestyle Alteration intervention, or Biospecimen-Based or Imaging-Based Assessment tool), and identifies the population/cancer type in which it is to be tested.

Information Requested

This RFI invites input from the scientific community on Translational Research Opportunities that follow the Immune Response Modifiers Pathway to testing in Phase I/II clinical trials (Clinical Cancer Research 14: 5692-5699, 2008, http://clincancerres.aacrjournals.org/cgi/reprint/14/18/5692.pdf). Information is sought from members of the scientific community at large, academic and non-academic translational cancer researchers, clinical oncologists, and investigators from the pharmaceutical/biotechnology industry. The opportunities can relate to a range of specific therapeutic regimens and target populations. Any information that can be shared regarding the immunogenicity and therapeutic function of an antigen, the scientific validity and feasibility of the formulation for that antigen, and/or the scientific validity and feasibility of combinations with immune modifier agents is requested. In addition, information on assays of

http://grants.nih.gov/grants/guide/notice-files/NOT-CA-09-031.html[7/21/2009 8:06:04 AM]

NCI prioritization of Immune Modifying Agents (2007)

http://dcb.nci.nih.gov/ImmunAgentWork

Top 20

NCI prioritization of 75 cancer antigens: *Clin Can Res, 15: 5323, 2009*

Top 15

Gather IRM Translational Research Opportunities: **TSM and TSM2**

NCI-wide Translational Science Meeting

- **November 7-9, 2008, Washington, DC**
  - **513 posters**
    - Grants/PIs selected by NCI program staff
  - **800 invited participants**
    - NCI-funded scientists/clinicians
    - Advocates
    - NCI staff

23 IRM abstracts

- **TSM2: November 5-7, 2009, Vienna, VA**
  - **423 posters**
  - **>750 participants**
  - Added cross-pathway Panel Discussion sessions
  - Added open Satellite meetings

20 IRM abstracts

Process to Accelerate Translational Science Initiative

Gather information

↓

Prioritize

Which Opportunities are most “ripe” for acceleration?

↓

Fund & Manage

IRM Prioritization Working Group of CTAC

- Lisa Butterfield, *Univ Pittsburgh*
- Mac Cheever, *Fred Hutchinson*
- Nora Disis, *Univ Washington*
- Olivera Finn, *Univ Pittsburg*
- Elizabeth Jaffee, *Johns Hopkins*
- Carl June, *Univ Penn*
- David Peace, *Univ Illinois*
- Jane Reese-Coulbourne, *Advocate Partners*
- Wenru Song, *Pfizer*
- Mario Sznol, *Yale Univ*
- Louis Weiner, *Georgetown*

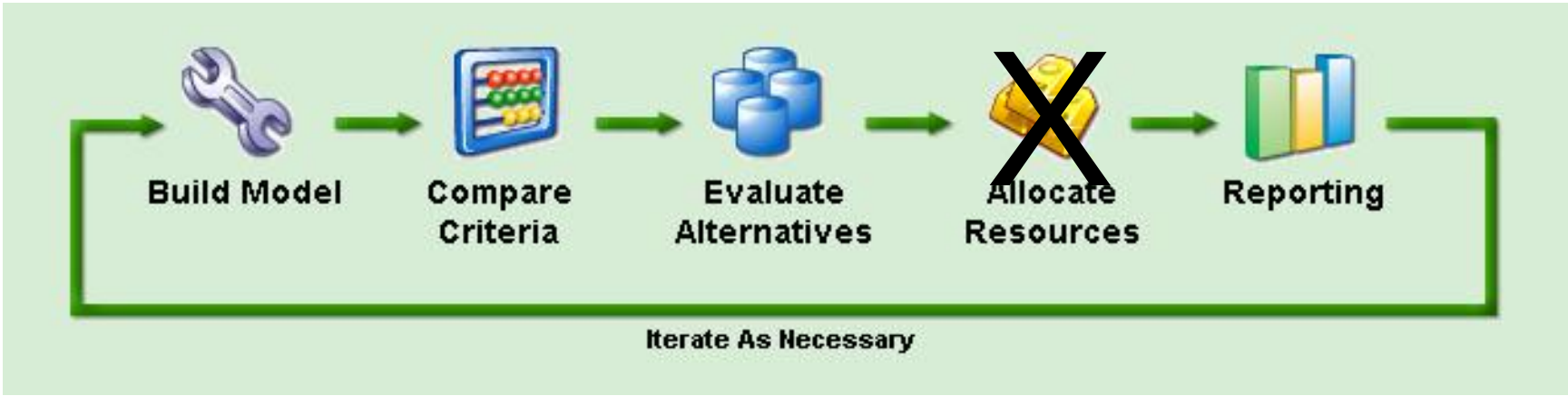
- Jay Berzofsky, *NCI CCR*
- Francesco Marincola, *NIH CC*
- Nicholas Restifo, *NCI CCR*
- Giorgio Trinchieri, *NCI CCR*

- *Stephen Creekmore, *NCI, BRB*
- *Toby Hecht, *NCI, TRP*
- *Howard Streicher, *NCI, CTEP*

- Lynn Matrisian, *NCI, CCCT*
- *Tawab Amiri, *NCI, CCCT*

* NCI liaisons

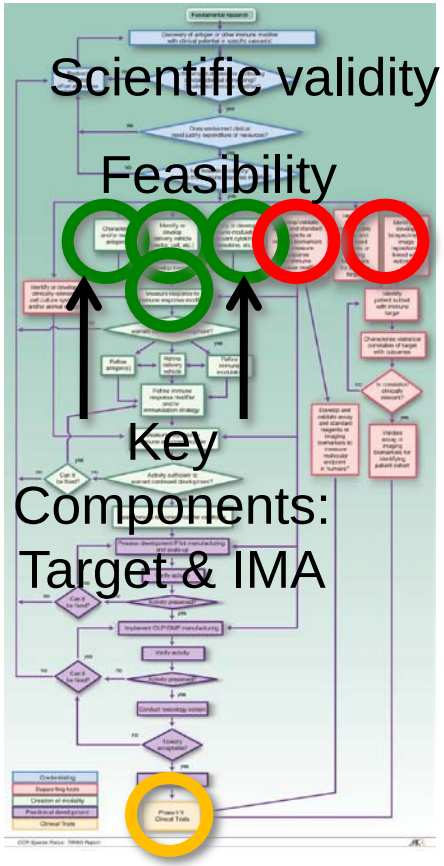
AHP/*Decision Lens* Prioritization Tool



- Web-based platform facilitates webinar discussion or asynchronous input
- Logical organization and tracking of alternatives
- Facilitates updates in information
- Facilitates transparency, discussion of disparate viewpoints
- Integrates objective and subjective evaluation
- Allows “what if” scenarios to increase confidence in ranking
- Allows evaluation of components in isolation
- Does NOT make decisions – facilitates evaluation of information

IRM Pathway Translational Research Opportunity Prioritization

- 113 IRM translational research opportunities (various # of components)
- Determined which components were represented in each opportunity
- Added key components from Antigen and IMA prioritization, others added by IRMP WG: 174 final key component candidates
- Ranked each component by:
  - Level of evidence on **Scientific Validity** of each component
    - Experiments in humans
    - Experiments in animals
    - In vitro experiments
  - Information on **Feasibility** of each component
    - Full scale manufacturing
    - Piloted manufacturing
    - Laboratory product
- Each component evaluated by 2-3 IRMP WG members
- Discrepancies discussed and resolved

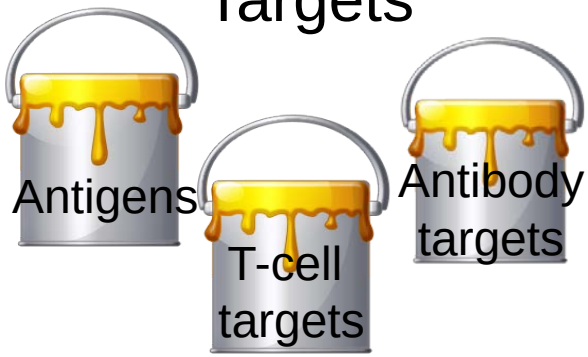


IRM Pilot Prioritization Project

Translational Science Meetings | **Request for Information** | **NCI-directed Workshops**

Translational Research Opportunities

Targets



Deconstruct

Key component candidates into ***buckets***

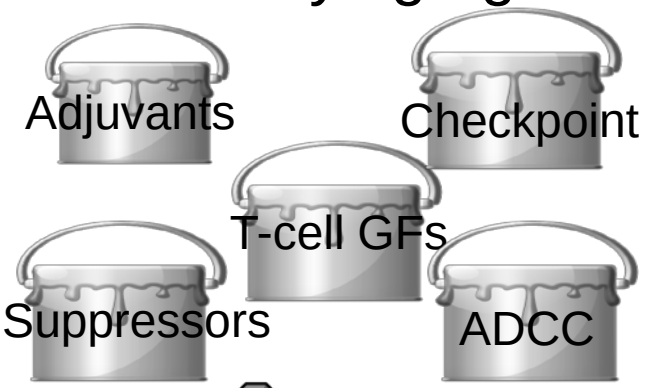
Prioritize

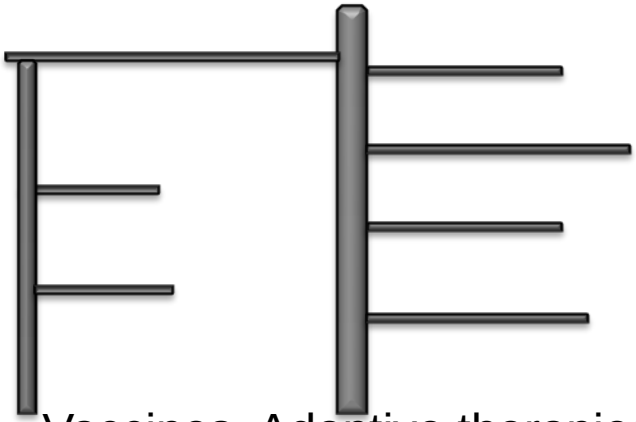
candidates within buckets

Reconstruct

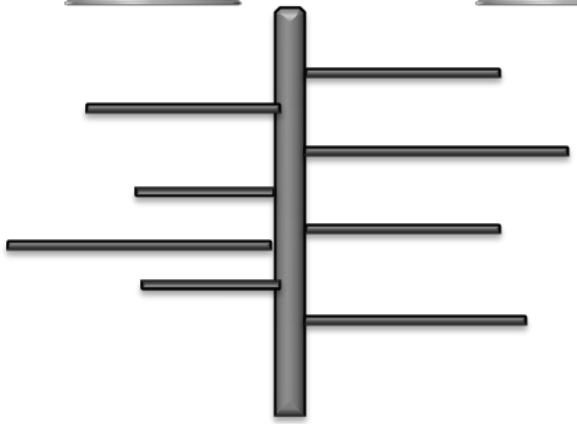
on ***scaffolds***

Immune modifying agents





Vaccines, Adoptive therapies



Antibodies, IMA combinations

Immune Response Modifier Pathway Prioritization Working Group Report

November 4, 2009

Martin A. (Mac) Cheever, M.D.

Immune Modifier Agents (IMA)

- Agents that mimic, augment or require participation of host immune cells for optimal effectiveness

Major Issue

- Phenomenal advances in basic immunology
- Discovery and invention of many agents with the potential to serve as immunotherapeutic drugs and cure patients with cancer
  - Many have been manufactured or could readily be manufactured
  - Many have great potential for benefiting cancer patients
    - **If** they were available for testing &
    - **If** focused funding were available for clinical trials to learn how to use them

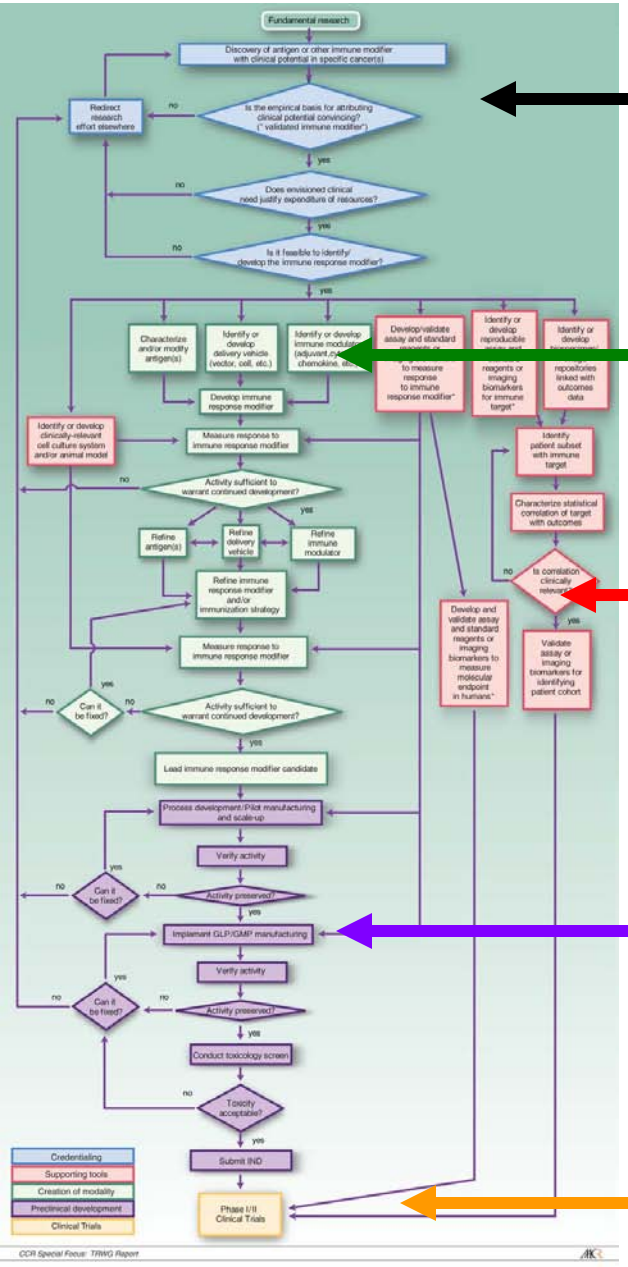
Major Issue

- Cancer vaccine example:
  - Discovered/invented/manufactured agents that could substantially improve cancer vaccines include:
    - Dendritic cell activators & growth factors
    - Vaccine adjuvants
    - T cell stimulators & growth factors
    - T cell attracting agents
    - Inhibitors of T cell checkpoint blockade
    - Inhibitors of immune cell & cancer cell suppression

Major Issue

- Antibody example:
  - Discovered/invented/manufactured agents that could substantially improve antibody therapy include:
    - Agents to increase antibody dependent cellular cytotoxicity (ADCC)
      - NK cell activators & growth factors
      - Dendritic cell activators & growth factors
      - Vaccine adjuvants (active innate immunity)
      - T cell stimulators & growth factors
      - T cell attracting agents

Immune Response Modifier Pathway



Credentialing
(Antigen Target & Immune Modifier Agent)

Creation of Modality
(Antigen + Formulation + Agent)

Supporting tools
(Assays to select patients)
(Assays to monitor response)

Development
(Scale-up & Manufacturing)

Clinical Trials

MANY Antigens & Agents have been moved down the Pathway

"Gap" is insufficient iterative early phase clinical trials to learn how to employ already discovered antigens & agents

“Gap” Barriers

- Concurrent development of several unapproved agents is exceedingly difficult
  - Many immune modifier agents are unlikely to work as monotherapy
- Funding mechanisms support best grants & best groups, not best trials possible

- STRAPS provide a mechanism for designing & funding the best trials possible
  - STRAPS can provide organizational structure & funding mechanisms for
    - Top prioritized trials
      - Access to prioritized standard agents & prioritized novel agents
    - Team of experienced investigators
    - Capacity to elucidate reasons for success or failure
      - Immune response & therapy monitoring
      - Assays for patient selection & correlates of response
    - Adequate “on-time” funding
    - Project management

Categories: Immune Response Modifier Pathway

- Vaccines
  - To activate and expand the number of patient T cells capable of specifically killing cancer cells
- Autologous T cell therapy
  - To treat with large numbers of cultured autologous T cells
- Antibody therapy
  - To augment the efficacy of “standard” antibody therapy
- Combinations of Immune Modifier Agents
  - To activate and expand nascent or ongoing autochthonous immune responses

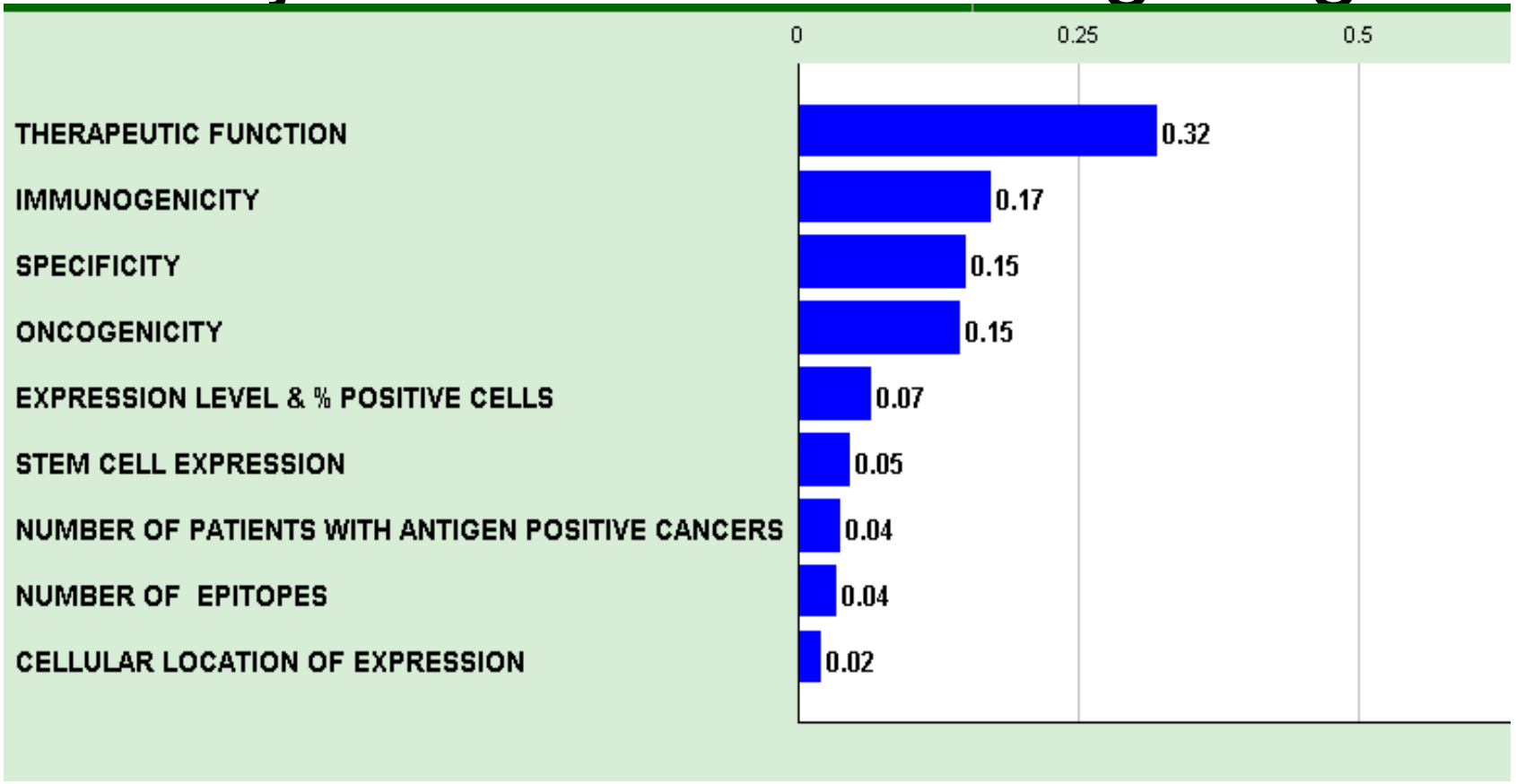
What vaccine regimen has the highest potential for success?

- Three components of cancer vaccine regimens to consider
  (1) Antigen Target
  (2) Immune modifying agents (IMAs) to induce & maintain immune response
  (3) Regimen
    - Antigen Target in combination with biologically defined IMA

- NCI workshops have piloted prioritization schemes
  - Antigens
    - Cancer Antigen Pilot Prioritization Project (October 2008)
  - Immune modifying agents
    - Immunotherapy Agents Workshop (July 2007)
      - Included adjuvants
  - Regimens (2009)
    - NCI Immune Response Modifier Pathway Prioritization Project
      - To develop an Immune Response Modifier STRAP (Special Translational Research Acceleration Project)

Cancer Antigen Prioritization

Major Criteria with Weighting

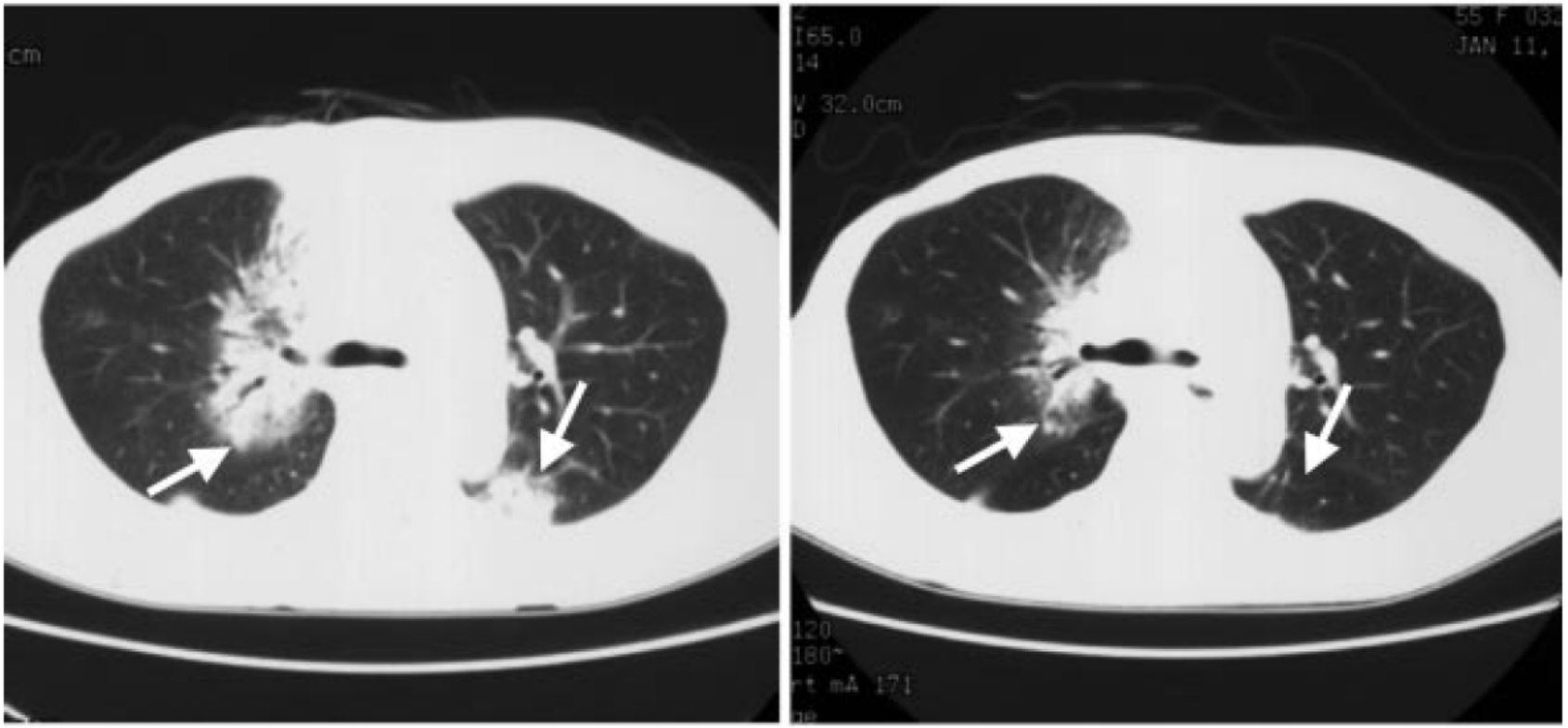


Clin Can Res, 15: 5323, 2009

Antigen Pilot Prioritization: Outcome

- None of the 75 antigens had all of the criteria/characteristics of the “ideal” cancer antigen.
- 20 had suggestive clinical efficacy
- 46 were immunogenic in clinical trials
- Outcome
  - Reflected the extent and vigor of the cancer vaccine field
  - Accentuated the need for prioritization.

WT1 Peptide-Based Vaccine – Induces CTL and Regressions in Some Patients

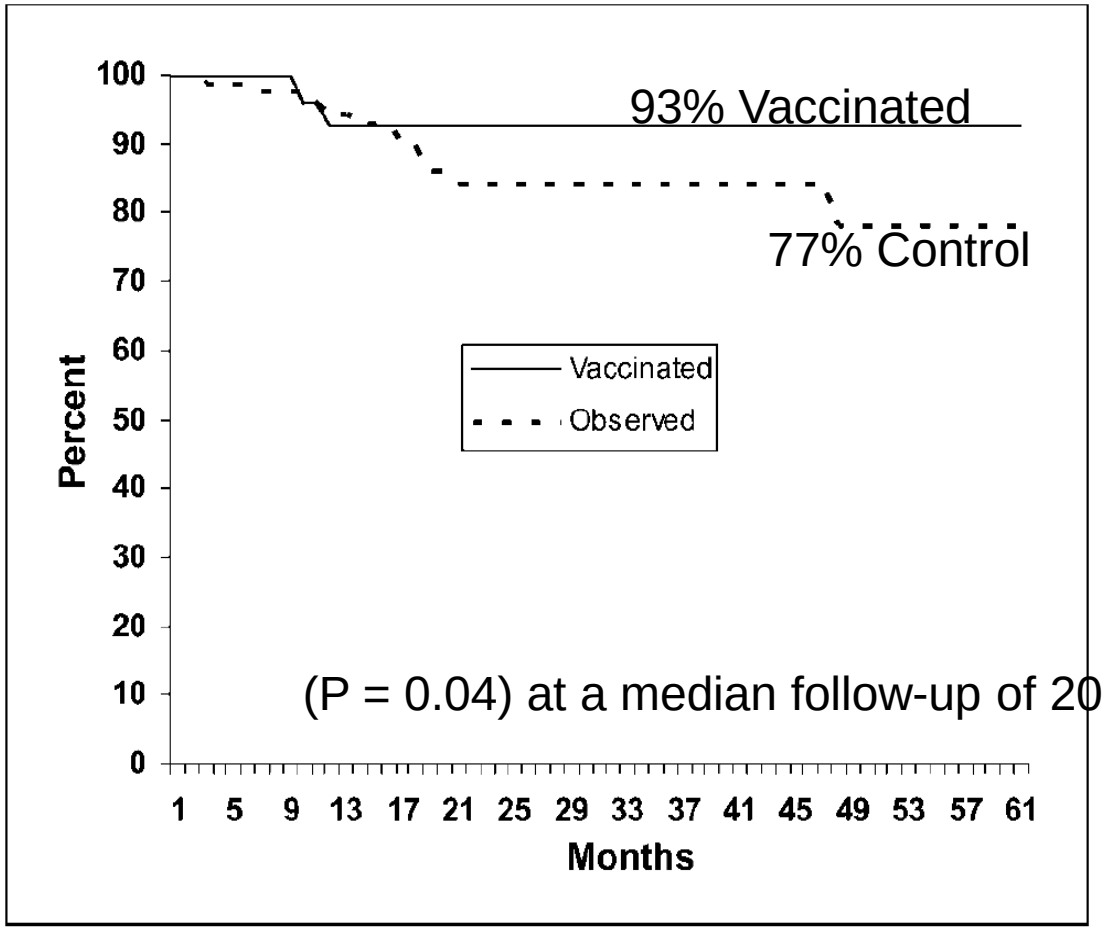


Tumor regression in patient with breast cancer.
CAT Scan before (*Left*) and after (*Right*) WT1 vaccination

[Oka et al PNAS 101:13885 (**2004)]**

HER2 Peptide-Based Vaccine

Kaplan-Meier disease-free survival curves at 20 month median follow-up (171 enrolled patients)



(P = 0.04) at a median follow-up of 20 months

Previously treated disease free at time of vaccination

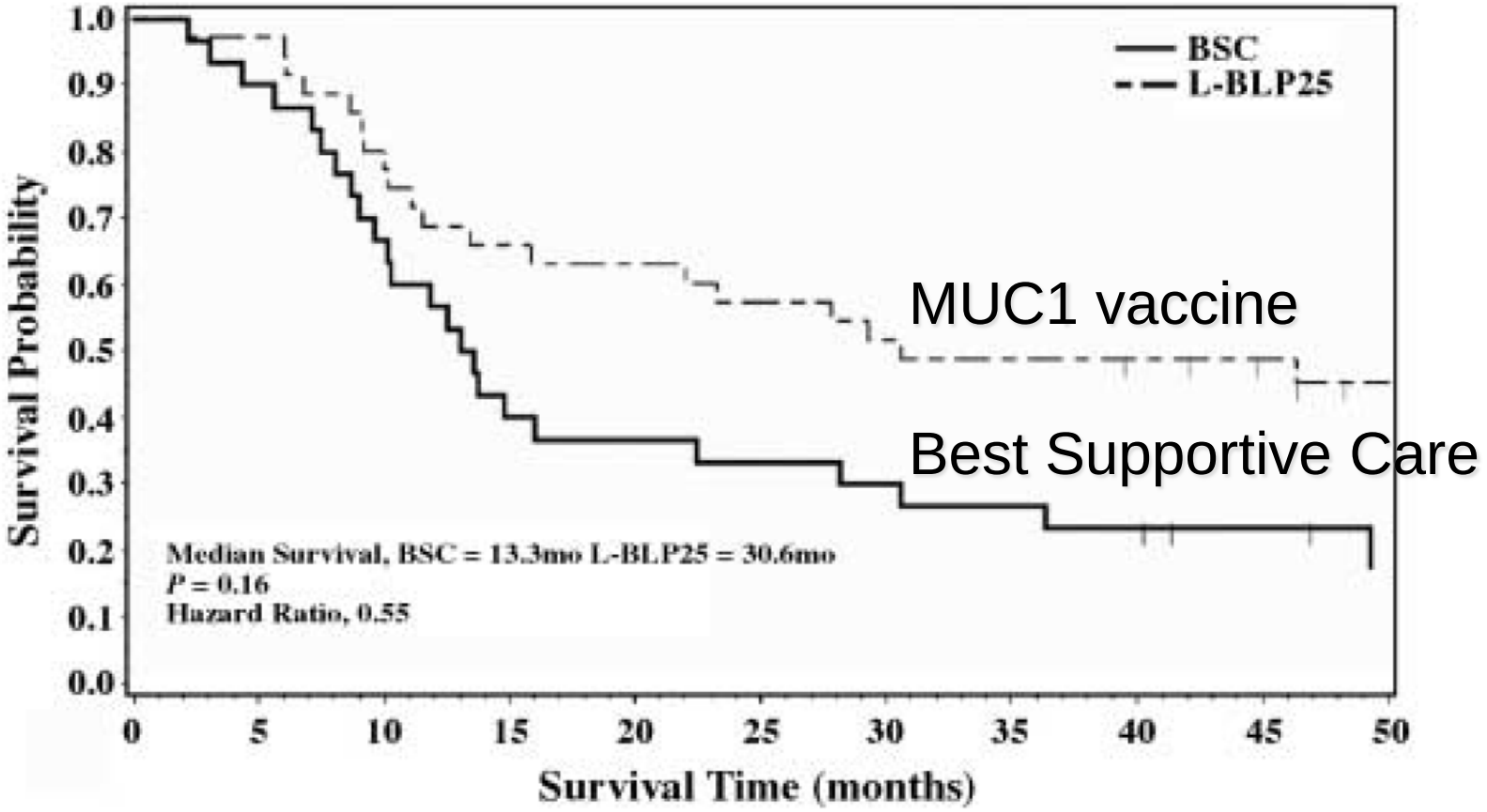
Planned analysis at 20 months

Randomized on expression of HLA-A2

[Peoples et al Clin Cancer Res 2008;797 14(3) February 1, 2008]

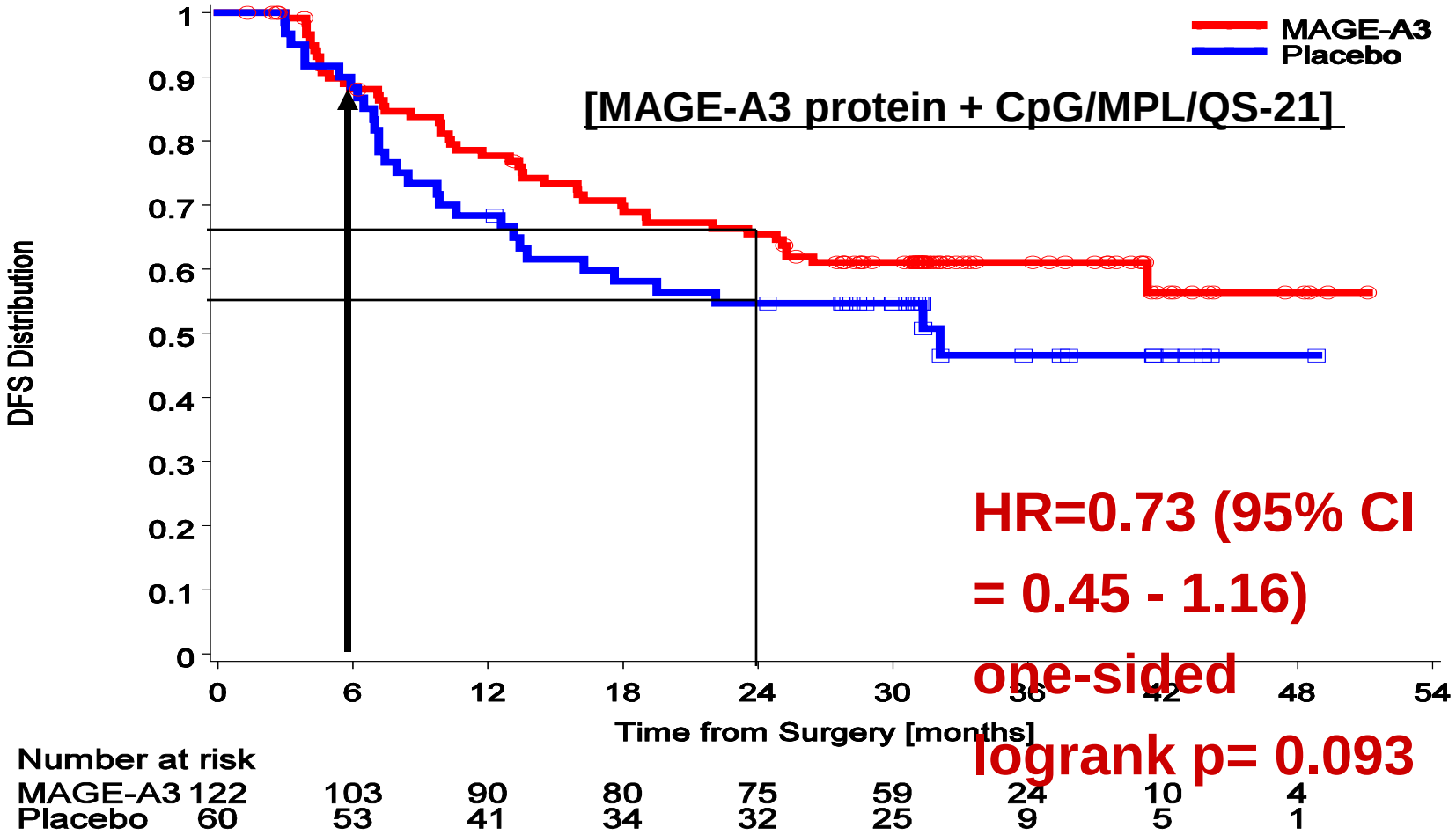
MUC1 Peptide-Based Vaccine: Advanced Stage NSCLC

- **Randomized Phase II**
- **MUC1 peptide vaccine vs. best supportive care**
- **Stage IIIB or IV; stable or responding to therapy**
- **Median survival, 30.6 versus 13.3 months; P = 0.16**



[Sangha & Butts Clin Cancer Res 13: 4652s 2007]

MAGE-A3 Protein-Based Vaccine – Randomized Phase II Adjuvant Trial in Early Stage NSCLC



DFS: Interval from the date of surgical resection to the date of recur

What vaccine regimen has the highest potential for success?

- NCI workshops have piloted prioritization schemes
  - Antigens
    - Cancer Antigen Pilot Prioritization Project (October 2008)
  - Immune modifying agents
    - Immunotherapy Agents Workshop (July 2007)
      - Included adjuvants
  - Regimens (Ongoing - 2009)
    - NCI Immune Response Modifier Pathway Pilot Project
      - To develop an Immune Response Modifier STRAP (Special Translational Research Acceleration Project)

NCI Workshop to Prioritize Immunotherapy Agents with High Potential for Cancer Therapy (July 12th 2007)

- Developed a ranked list of agents with high potential for use in cancer therapy
  - Exceedingly broad input & well-vetted
- Substantial demonstrated immunological efficacy
- Not broadly available for testing in patients with cancer
- Many already tested in clinical trials in patients with cancer
  - Proven substantial effects in activating, augmenting or sustaining human immune responses
  - Cancer was not eliminated when tested as monotherapy

Basic Tenants of T cell Immunity

- T cell repertoire needs to be infinite
- T cells expansion needs to be strictly limited
  - Limiting T cell growth factor concentration
  - Upregulation of T-cell checkpoint blockade
  - Induction of regulatory/suppressor cells
- Agents to circumvent limitations are available

Prioritization of Agents: List of agents with high potential for cancer therapy

- **T cell growth factors**
  - IL-7 (naïve T cells) [#5]
  - IL-15 (effector T cells) [#1]
  - IL-21 (T cells & NK) [#21]
    - **[Not on original list]**
- **DC activators**
  - Anti-CD40 & CD40L [#4]
- **DC growth factors to increase body burden of DC**
  - Flt3L [#11]
- **Vaccine adjuvants with immunotherapeutic potential**
  - IL-12 [#3]
  - CpG [#6]
  - MPL [#14]
  - Poly I:C [#15]
  - Resiquimod & 852A [#18]
- **T cell stimulators**
  - 4-1-BB (CD137) [#8]
  - Anti-GITR [#12]
  - Anti-OX40 [#16]
- **T-cell attracting chemokines**
  - Adv-CCL21 [#13]
- **Inhibitors of T cell checkpoint blockade**
  - Anti-PD1 & PD1Ligand [#2]
  - Anti–B7-H4 [#17]
  - Anti–LAG-3 [#19]
  - LIGHT [#20]
- **Inhibitors of cancer cell & immune cell suppression**
  - 1-methyl tryptophan (IDO inhibitor) [#7]
  - Anti-TGF-b [#9]
  - Anti-IL10 & Anti-IL10R [#10]

[Anti-CTLA4 not considered, presumed to be approved in near future]

http://web.ncifcrf.gov/research/brb/site/home.asp

What vaccine regimen has the highest potential for success?

- NCI workshops have piloted prioritization schemes
  - Antigens
    - Cancer Antigen Pilot Prioritization Project (October 2008)
  - Immune modifying agents
    - Immunotherapy Agents Workshop (July 2007)
      - Included adjuvants
  - Regimens (2009)
    - NCI Immune Response Modifier Pathway Pilot Project
      - To develop an Immune Response Modifier STRAP (Special Translational Research Acceleration Project)

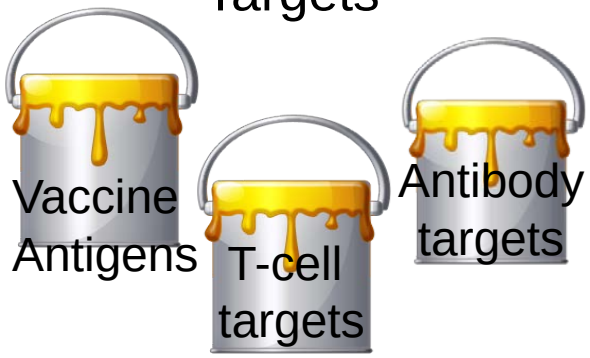
GOAL: of IRM Pathway Prioritization Working Group Select "Best" Immunotherapy Regimens for Development

- Cancer vaccines
  - Antigen
  - Adjuvant/Formulation
  - IMA to expand/maintain T cell response (i.e., area under curve - AUC)
  - Assays to monitor outcome – immune response qual & quant /tumor response
- T cell therapy
  - Antigen target
  - Vaccine to expand T cells prior to culture
    - (or recombinant T-cell receptor)
  - Vaccine & IMA post transfer to expand & maintain number of T cells
    - (i.e., area under curve - AUC)
  - Assays to monitor outcome – immune response/tumor response
- Ab therapy
  - Ab
  - IMA to augment ADCC
- IMA Combinations
  - Several synergistic immune response modifiers to activate then augment autochthonous responses
  - Assays to monitor outcome – immune response to specific designated antigens/tumor response

Translational Science Meetings | Request for Information | NCI-directed Workshops

Translational Research Opportunities

Targets



Deconstruct

Key component candidates into ***buckets***

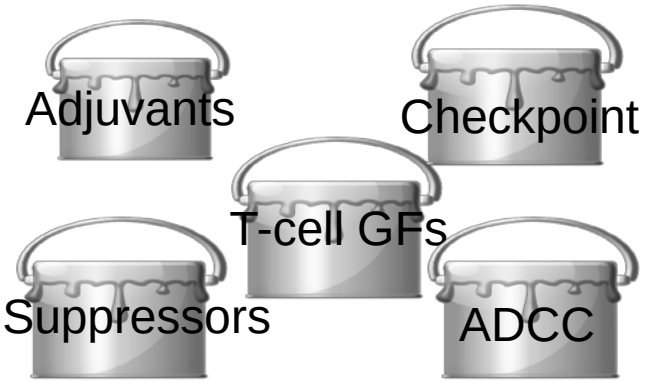
Prioritize

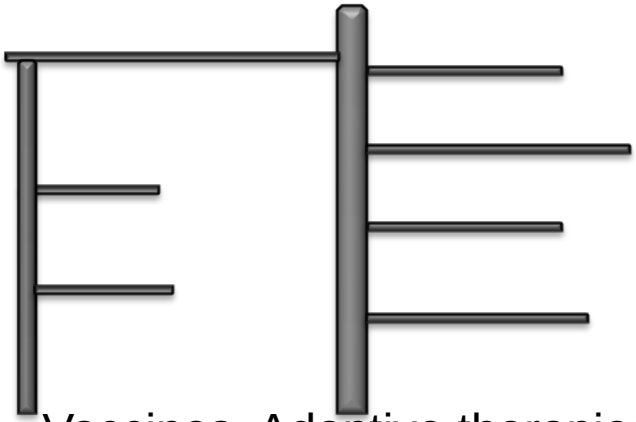
candidates within buckets

Reconstruct

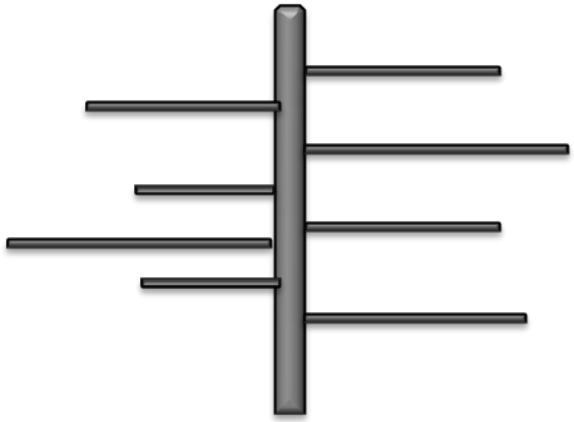
on ***scaffolds***

Immune modifying agents





Vaccines, Adoptive therapies

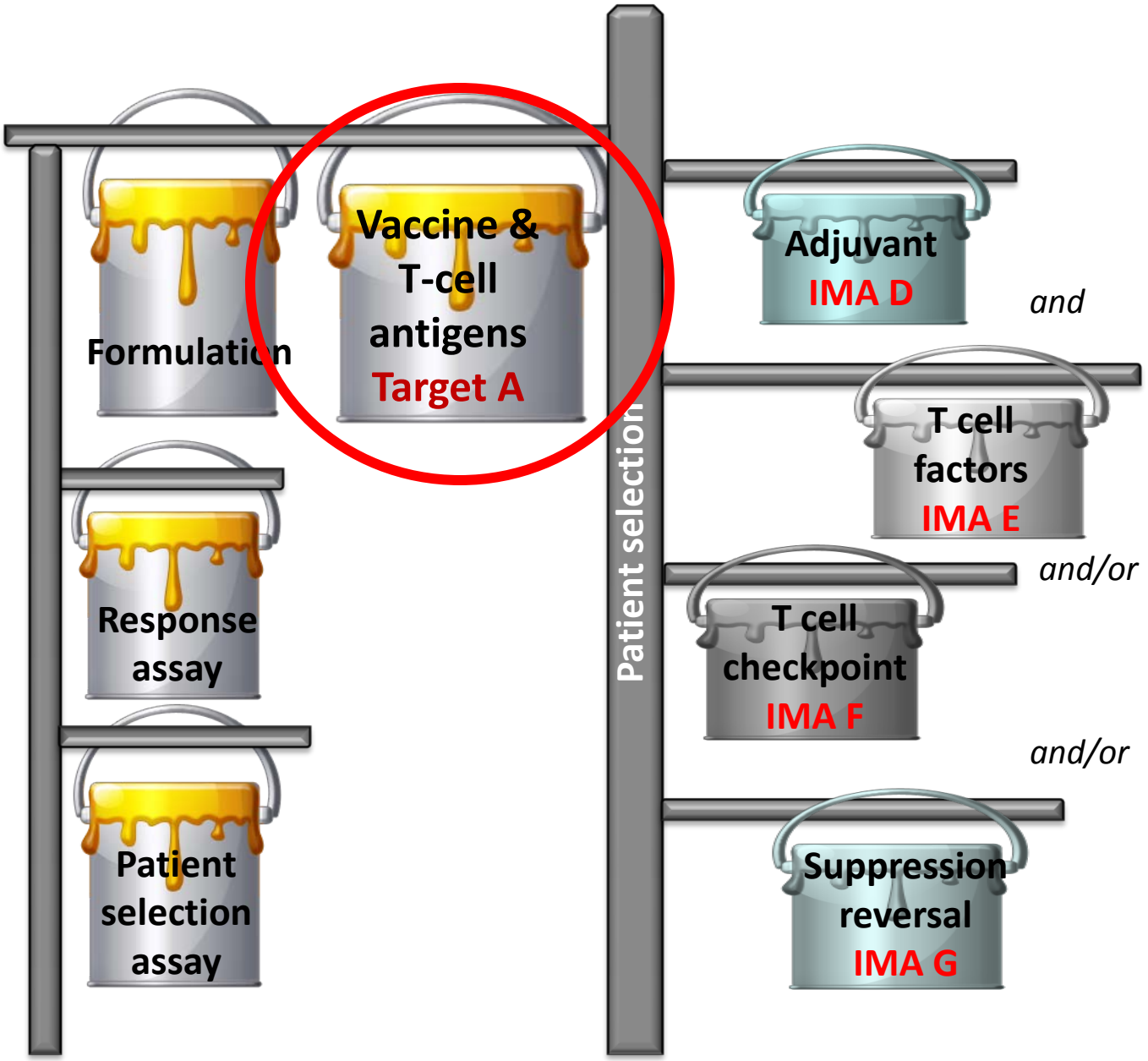


Antibodies, IMA combinations

Working Group Prioritized Targets & Agents

REGIMEN	**TARGET**	**IMA** *(one or more of the following)*
Cancer Vaccines	A: Vaccine Antigens	D: Adjuvants (required) E: T-cell factors, and/or F: Checkpoint inhibitors, and/or G: Suppressive agents
Adoptive Therapy	B: T-cell therapy antigens	E: T-cell factors and/or F: Checkpoint inhibitors
Antibody Therapy	C: Antibody & T-body antigens	H: ADCC
IMA Combinations		Combinations of the above

CANCER VACCINE SCAFFOLD



What vaccine regimen has the highest potential for success?

Select a cancer antigen with a high potential for success

- Top 15 antigens from Cancer Antigen Pilot Prioritization Project (Oct 2008)
- Vaccine targets from Response to RFI NOT-CA-09-031
- Vaccine targets from NCI Translational Science meeting abstracts, 2008 and 2009

- Evaluated for Therapeutic Efficacy and Immunogenicity (priority score)
- Further evaluated for appropriateness for STRAP
  - Antigens must be defined
  - Antigens must be represented on enough tumors to accrue patients for clinical trials in a reasonable amount of time
  - Approach should not be “overripe”, i.e. ready for Phase III trials

Target A: Vaccine and T-cell antigens

Project	Candidate	Bucket	Rank	Comment
R028 CpG-MCL vaccine/ATC therapy (lymphoma)	CpG-activated, autologous whole-cell MCL	A	1.00	antigens not defined, patient specific
R016 Shed BrCa Ag, IL2 GM liposomes	Shed BrCa Ag	A	1.00	antigens not defined
R006 Auto tumor transfected w IGFR antisense (Astrocytoma)	Auto tumor/IGF-1R/AS ODN	A	1.00	patient specific
T1-334 MinorHA alloTcells CD3/CD28/IL2 expand (lymphoma)	MinorHA allo	A	1.00	antigens not defined
T1-343 MinorHA alloTh2 HSCT	Allogeneic hematologic malignanc shared antigens	A	1.00	antigens not defined
T1-342 Unique/shared autoTIL Lymph/deplet IL2 melanoma	Autologous tumor shared antigens	A	1.00	antigens not defined, patient specific
T2-302 Auto tumor + proteasome inhibitor (NSCLC)	Auto tumor	A	1.00	antigens not defined, patient specific
T1-522 HPV DNA by electroporation	HPV E6/7	A	0.93	(#4 on antigen list)
T1-542 HPV E6/7 DNA + vaccinia (higrade CIN2/3)	HPV E6/7	A	0.93	
A001 HPV E6/E7	HPV E6/E7	A,B	0.93	
R004 Anti-HER2 fused to LIGHT protein	HER2	A	0.90	(#6 on antigen list)
T2-030 Allo tumor/GM + Cy + Doxorubicin (BrCa)	HER2	A	0.90	
T1-546 HER2 Adv (EC +TM domain) + DC for BrCa	HER2	A	0.90	
T2-154 HER2 heterologous DNA	HER2 heterologous DNA	A	0.90	
A002 HER-2/neu	HER2	A,B	0.90	
A003 MAGE A3	MAGE A3	A	0.86	(#8 on antigen list)
T2-112 MelanA/MART1 recombTCR + PET reporter	MelanA/MART1	A	0.85	
A004 MelanA/MART1	MelanA/MART1	A,B	0.85	
A014 gp100	gp100	A,B	0.84	
R034 gp100/OX40mAB/HD IL-2 (melanoma)	gp100+Trp2	A	0.84	
R039 gp100/Trp2 + Hsp110 complex (melanoma)	gp100+Trp2	A	0.84	
T1-545 Heterol gp100/TYRP2/GM-CSF DNA particle	Heterol gp100/TYRP2	A	0.84	
R025 Melanoma peptide-pulsed IL-15DC for melanoma/IL7	(MART-1+ gp100+ MAGE-A3+ tyrosinase)	A	0.84	
T2-226 Adv Tyrosinase/MART1/MAGE-A6 + DC	Adv Tyrosinase+MART1+MAGE-A6	A	0.84	
A008 MUC1	MUC1	A,B	0.84	Include, #2 in antigen list
T1-530 MUC1 peptides w Tn carbohydrate (BrCa)	MUC1	A	0.84	
T1-538 EGFRvIII peptide vac + temozolomide (GBM)	EGFRvIII	A	0.84	#5 on antigen list, not included because small subset of patients
A005 EGFRvIII protein	EGFRvIII	A	0.84	

HPV E6/E7

HER2

MAGE A3

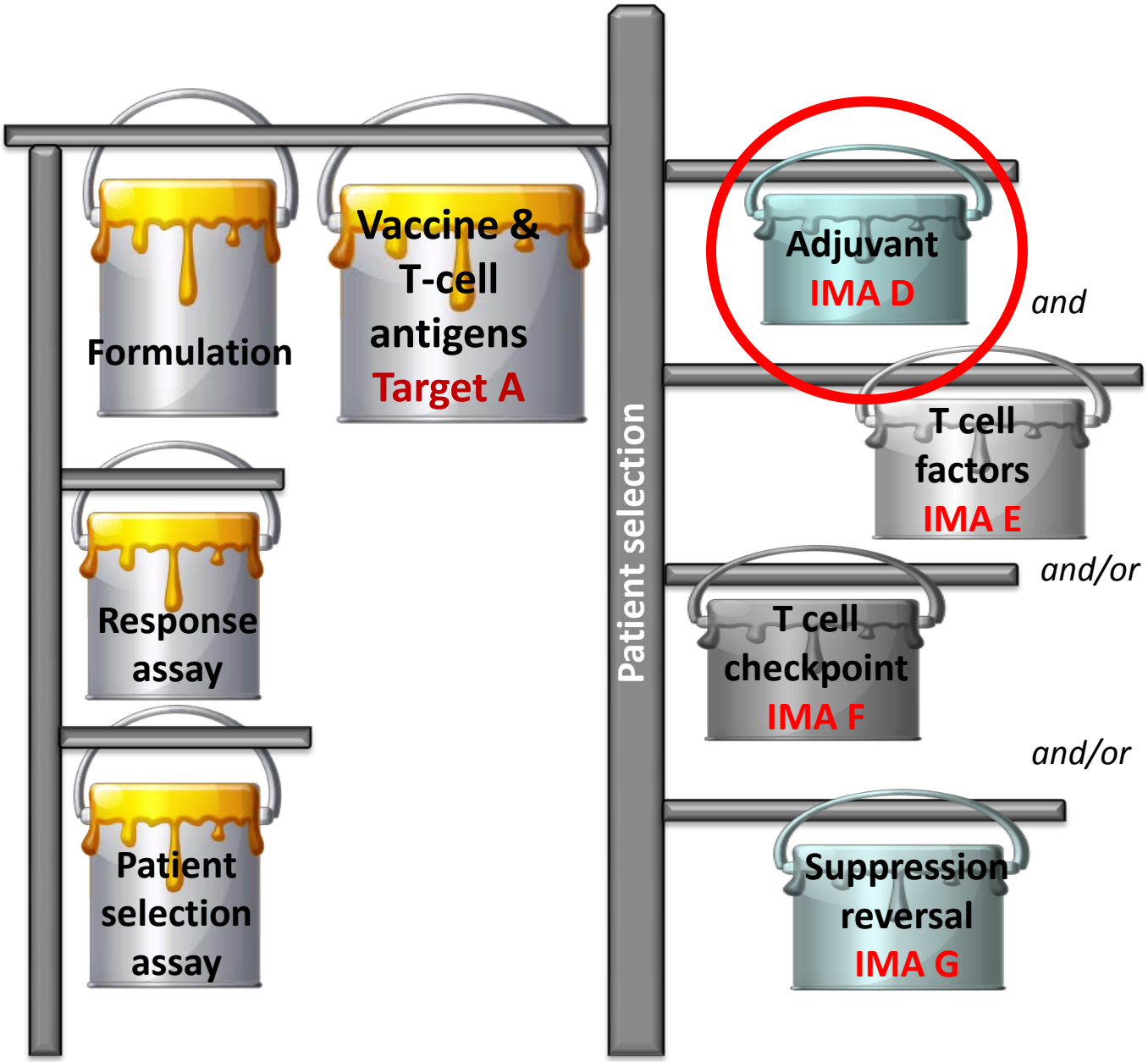
MUC1

Working Group Prioritized Targets & Agents

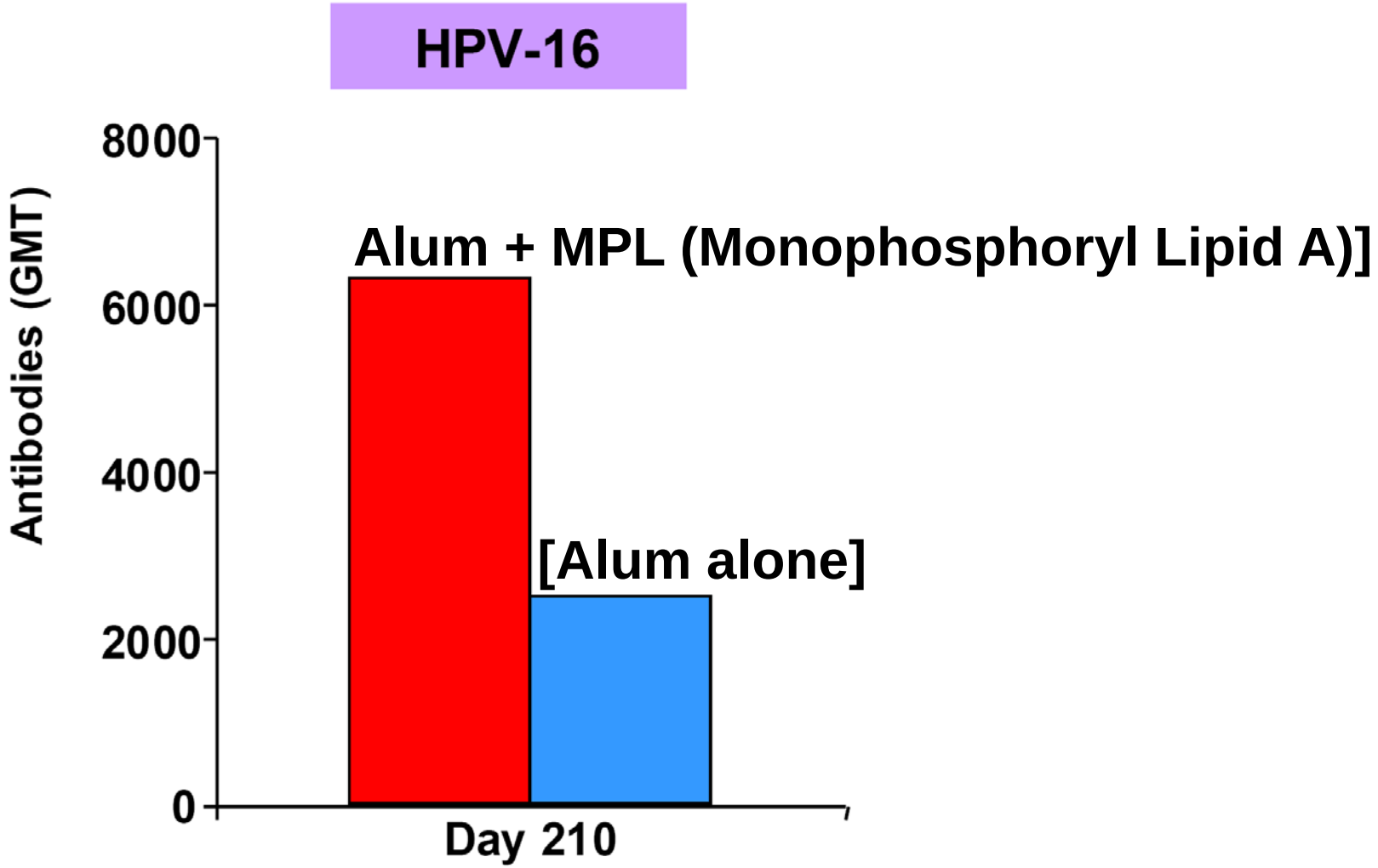
- **A: Vaccine Targets**
  - **HER2, HPV E6/7, MUC1, MAGE A3, WT1, NY-ESO-1, PSA**
- B: T-Cell Therapy Targets:
  - HER2, HPV E6/7, MUC1, MAGE A3, WT1, NY-ESO-1, PSA
- C: Antibody & T Body Targets
  - HER2, EGFR, CD20, CD19

- D: IMA: Vaccine adjuvants, dendritic cell activators, T cell attracting chemokines, or DC growth factors
  - CpG, CD40, IL-12
- E: IMA: T cell stimulators or T cell growth factors
  - IL7, IL21, IL15, Anti-4-1BB
- F: IMA: Inhibitors of T cell checkpoint blockade
  - Anti-CTLA-4, Anti-PD1
- G: IMA: Agents to neutralize or inhibit suppressive cells, cytokines, and enzymes
  - Anti-TGF beta, IDO inhibitors, Anti-IL10
- IMA H: Agents to increase antibody dependent cellular cytotoxicity (ADCC)
  - IL7, CpG, Anti-CD40, IL12, Anti-4-1BB or chimeric antibody receptors (CAR)

CANCER VACCINE SCAFFOLD



HPV Vaccine – Antibody Response



[JP Garnier, GSK CEO, Corporate Media Presentation Feb, 2005]

D: IMA: Vaccine adjuvants, dendritic cell activators, T cell attracting chemokines, or DC growth factors

- Adjuvants
  - Mandatory to achieve highest levels of response
    - Many choices
    - Best not defined
    - No “standard” adjuvant regimen
    - Dearth of adequate adjuvants for current trials
- NCI Agent Workshop provided list of 20 priority IMAs
  - 8 of 20 were deemed effective adjuvants
- Four prioritized by IRMP Working Group
  - Anti-CD40 & CD40L (DC Activator)
  - IL-12 (Vaccine Adjuvant)
  - CpG (Vaccine Adjuvant)
  - CCL21 (T cell attracting chemokine)
- Others on NCI Agent Workshop list
  - IL7, Flt3L, MPL, poly I:C, resiquimod
- Adjuvants need to be supplied to most investigators
  - Will require iterative human in vivo testing for most antigen formulations

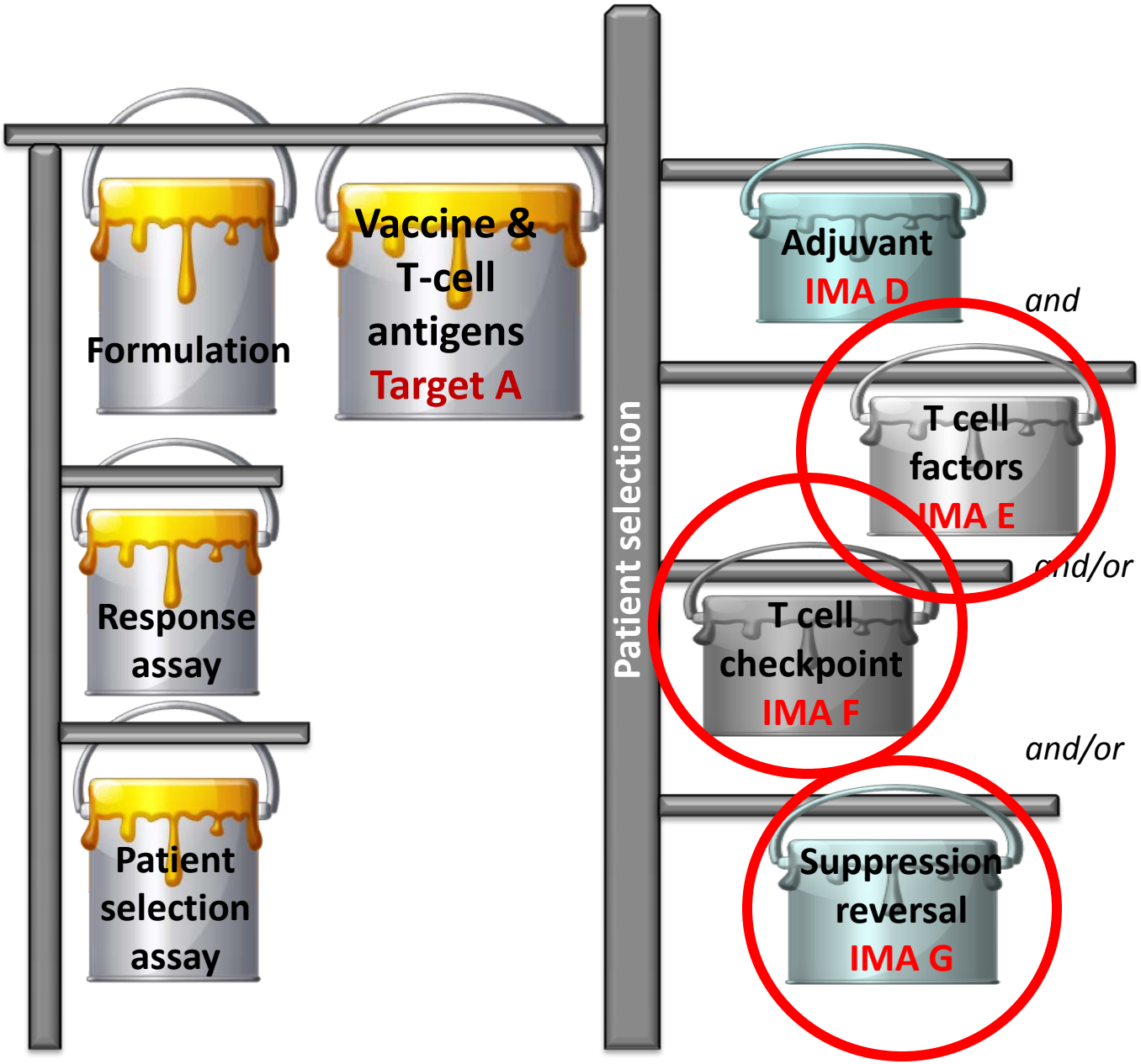
Working Group Prioritized Targets & Agents

Select an adjuvant with a high potential for success

- **A: Vaccine Targets**
  - **HER2, HPV E6/7, MUC1, MAGE A3, WT1, NY-ESO-1, PSA**
- B: T-Cell Therapy Targets:
  - HER2, HPV E6/7, MUC1, MAGE A3, WT1, NY-ESO-1, PSA
- C: Antibody & T Body Targets
  - HER2, EGFR, CD20, CD19

- **D: IMA: Vaccine adjuvants, dendritic cell activators, T cell attracting chemokines, or DC growth factors**
  - **CpG, CD40, IL-12**
- E: IMA: T cell stimulators or T cell growth factors
  - IL7, IL21, IL15, 4-1BB
- F: IMA: Inhibitors of T cell checkpoint blockade
  - anti-CTLA-4, Anti-PD1
- G: IMA: Agents to neutralize or inhibit suppressive cells, cytokines, and enzymes
  - Anti-TGF beta, IDO inhibitors, anti-IL10
- IMA H: Agents to increase antibody dependent cellular cytotoxicity (ADCC)
  - IL7, CpG, Anti-CD40, IL12, 4-1BB or chimeric antibody receptors (CAR)

CANCER VACCINE SCAFFOLD



Working Group Prioritized Targets & Agents

Select an IMA with a high potential for success

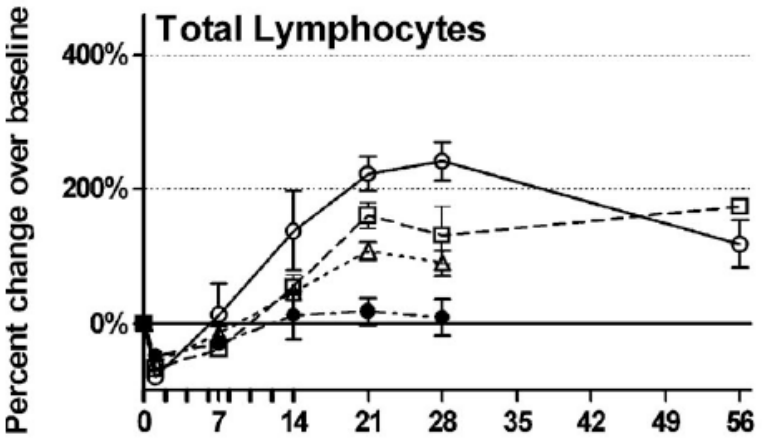
- **A**: Vaccine Targets
  - HER2, HPV E6/7, MUC1, MAGE A3, WT1, NY-ESO-1, PSA
- B: T-Cell Therapy Targets:
  - HER2, HPV E6/7, MUC1, MAGE A3, WT1, NY-ESO-1, PSA
- C: Antibody & T Body Targets
  - HER2, EGFR, CD20, CD19

- D: IMA: Vaccine adjuvants, dendritic cell activators, T cell attracting chemokines, or DC growth factors
  - CpG, CD40, IL-12
- **E: IMA: T cell stimulators or T cell growth factors**
  - **IL7, IL21, IL15, Anti-4-1BB**
- F: IMA: Inhibitors of T cell checkpoint blockade
  - Anti-CTLA-4, Anti-PD1
- G: IMA: Agents to neutralize or inhibit suppressive cells, cytokines, and enzymes
  - Anti-TGF beta, IDO inhibitors, anti-IL10
- IMA H: Agents to increase antibody dependent cellular cytotoxicity (ADCC)
  - IL7, CpG, Anti-CD40, IL12, Anti-4-1BB or chimeric antibody receptors (CAR)

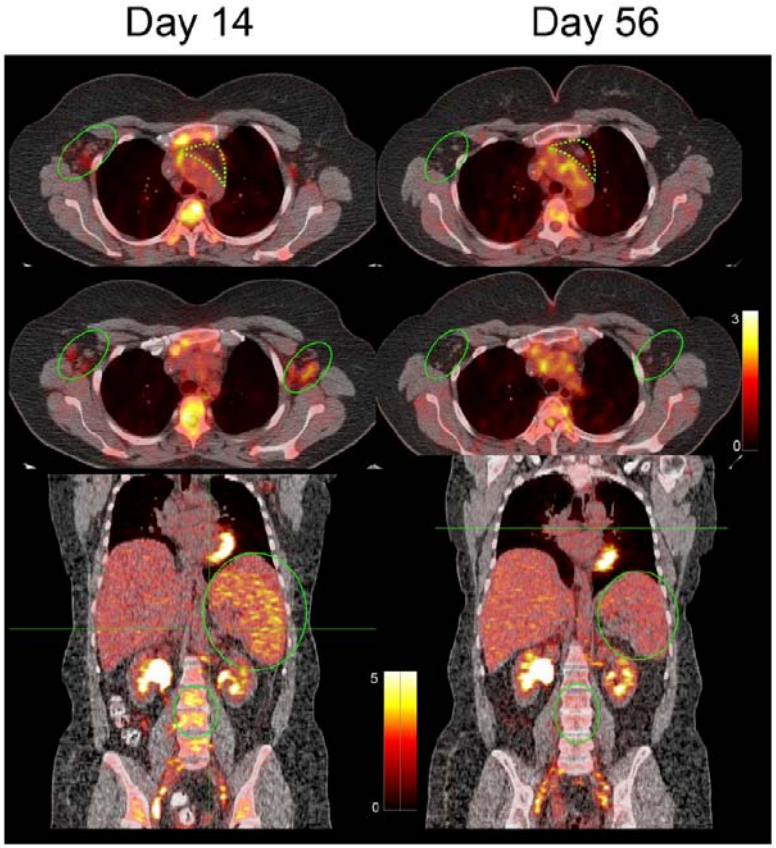
“Administration of rhIL-7 in humans increases in vivo TCR repertoire diversity by preferential expansion of naive T cell subsets”

IL-7 administered every other day (days 1 – 14) at 4 dose levels

IL-7 therapy increases circulating T cells



PET-CT imaging of lymphoid organs & increased metabolic activity after rhIL-7



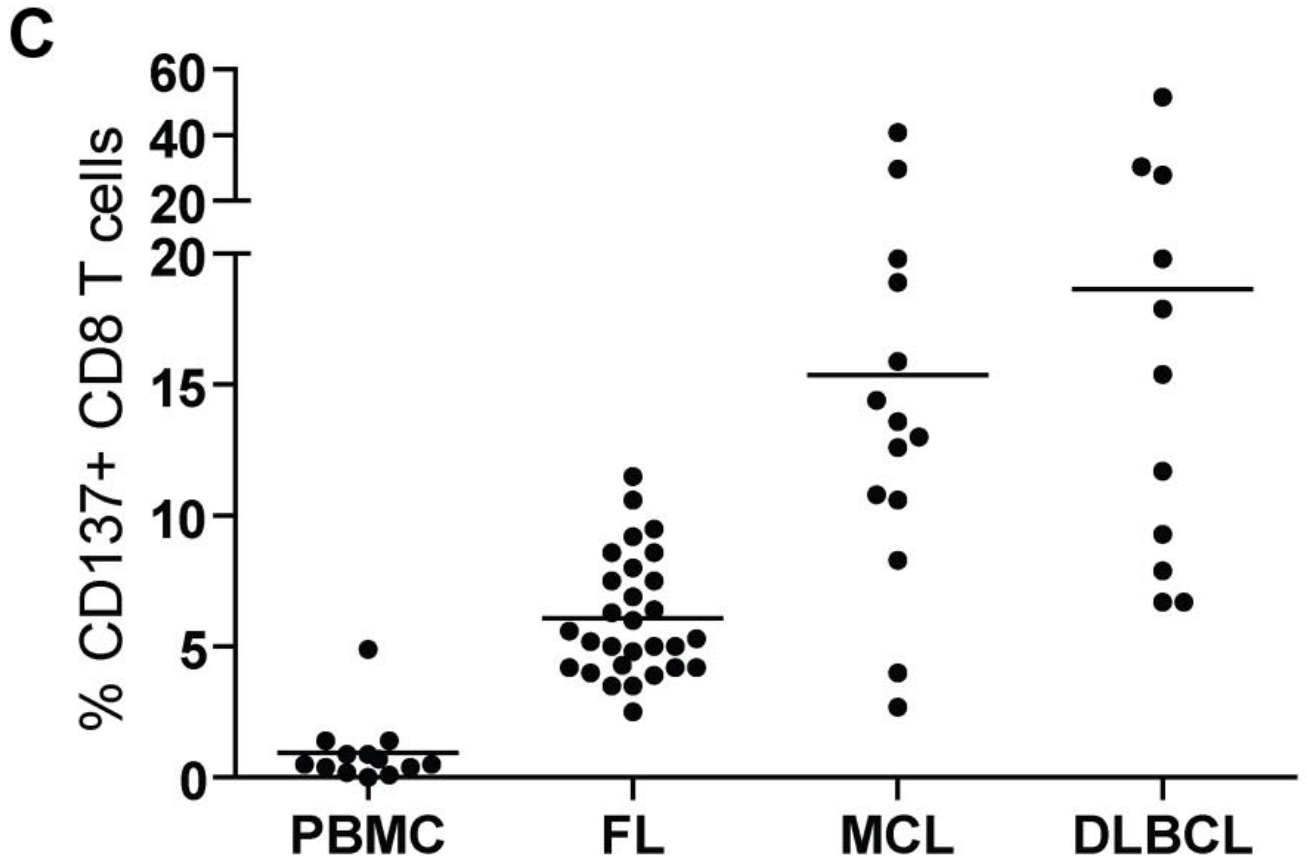
Increased metabolic activity = pink
Maximal = yellow

[Sportès (Mackall) et al J. Exp. Med. 1681:2007]

4-1BB (CD137)

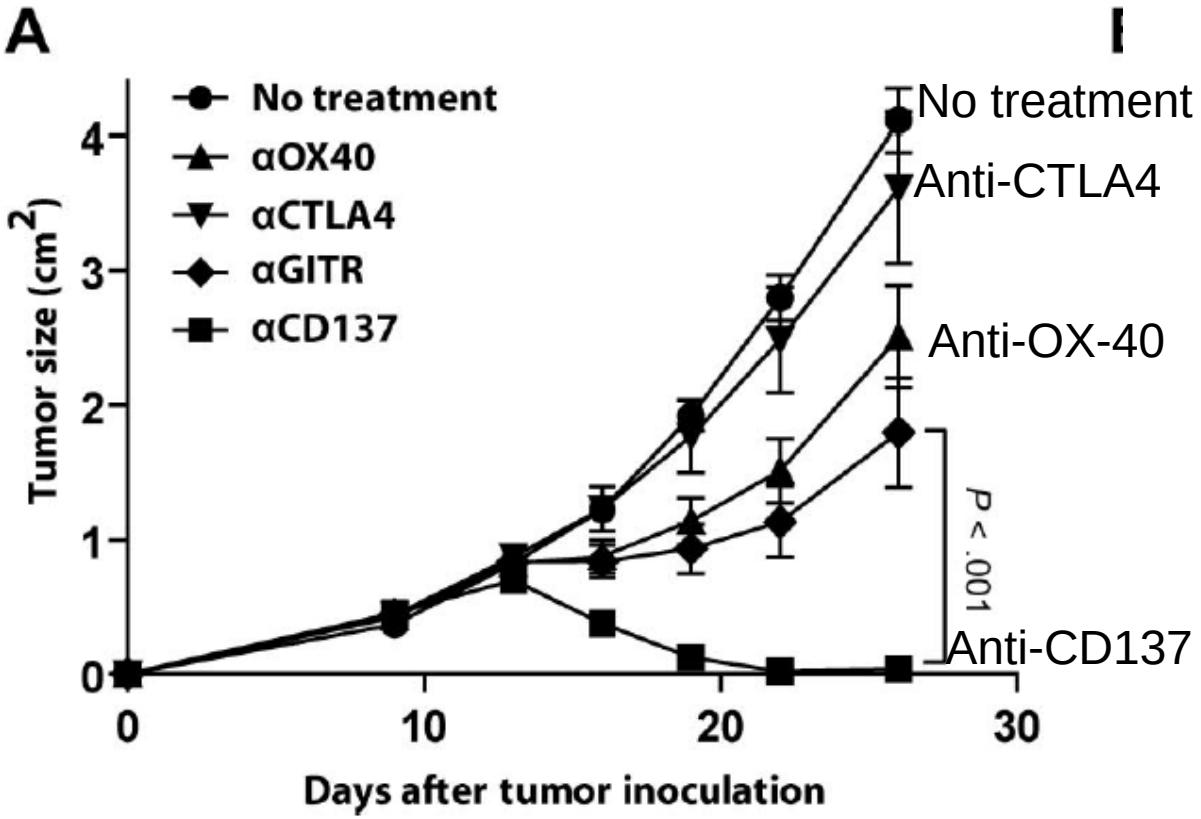
- Co-stimulatory receptor on T cells
  - Induced upon T-cell receptor (TCR) activation
- Agonist Ab (anti-CD137) leads to
  - Increased T-cell proliferation
  - Cytokine production
  - Functional maturation
  - Prolonged CD8 T-cell survival

Tumor-involved lymph nodes from lymphoma patients are infiltrated by CD137 T cells



[Houot et al (Levy) BLOOD 114:3431 2009]

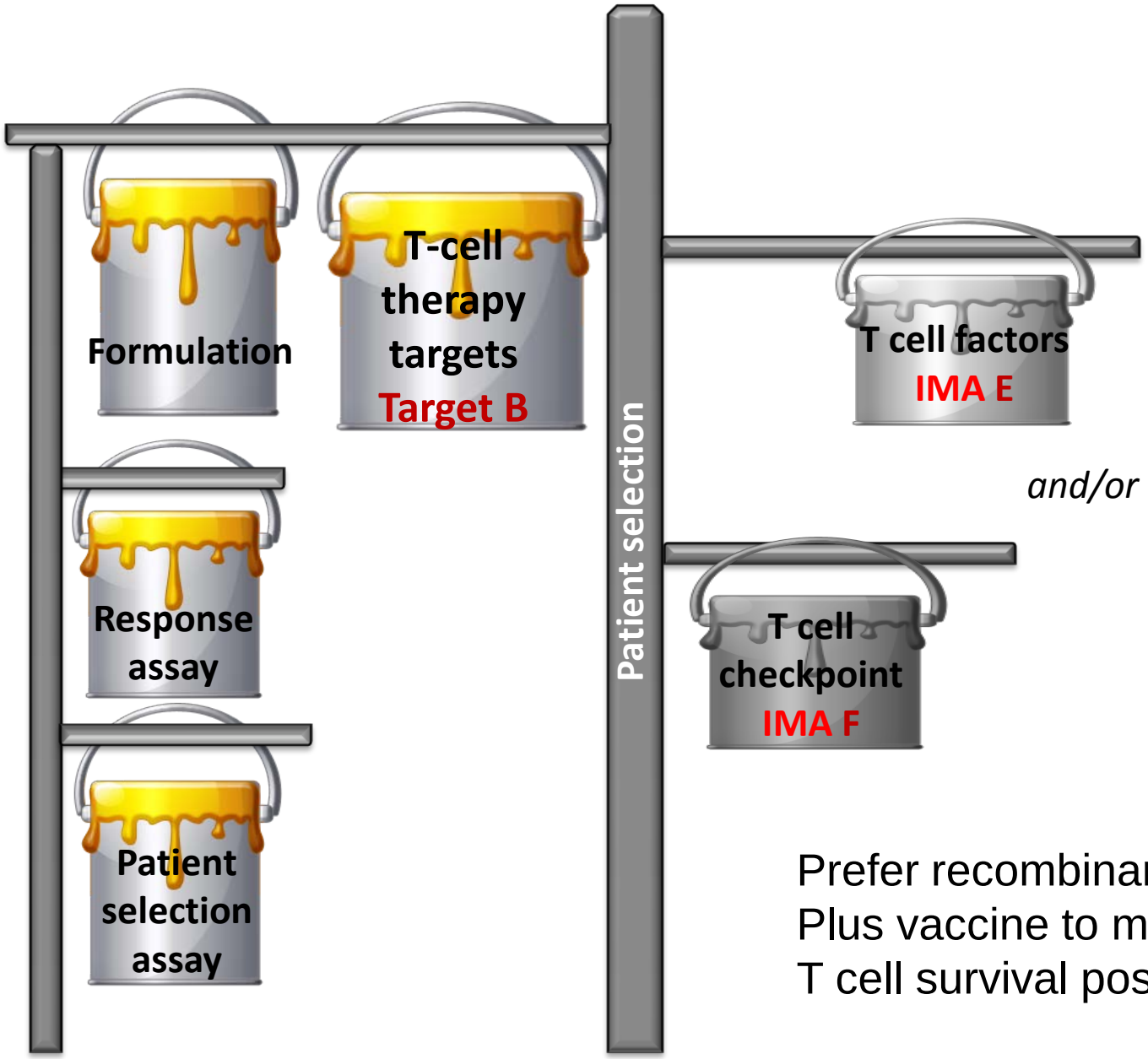
Anti-CD137 agonistic mAb has potent antilymphoma activity in vivo



BALB/c mice inoculated subcut with $5x10^6$ A20 tumor cells

[Houot et al (Levy) BLOOD 114:3431 2009]

ADOPTIVE THERAPY SCAFFOLD



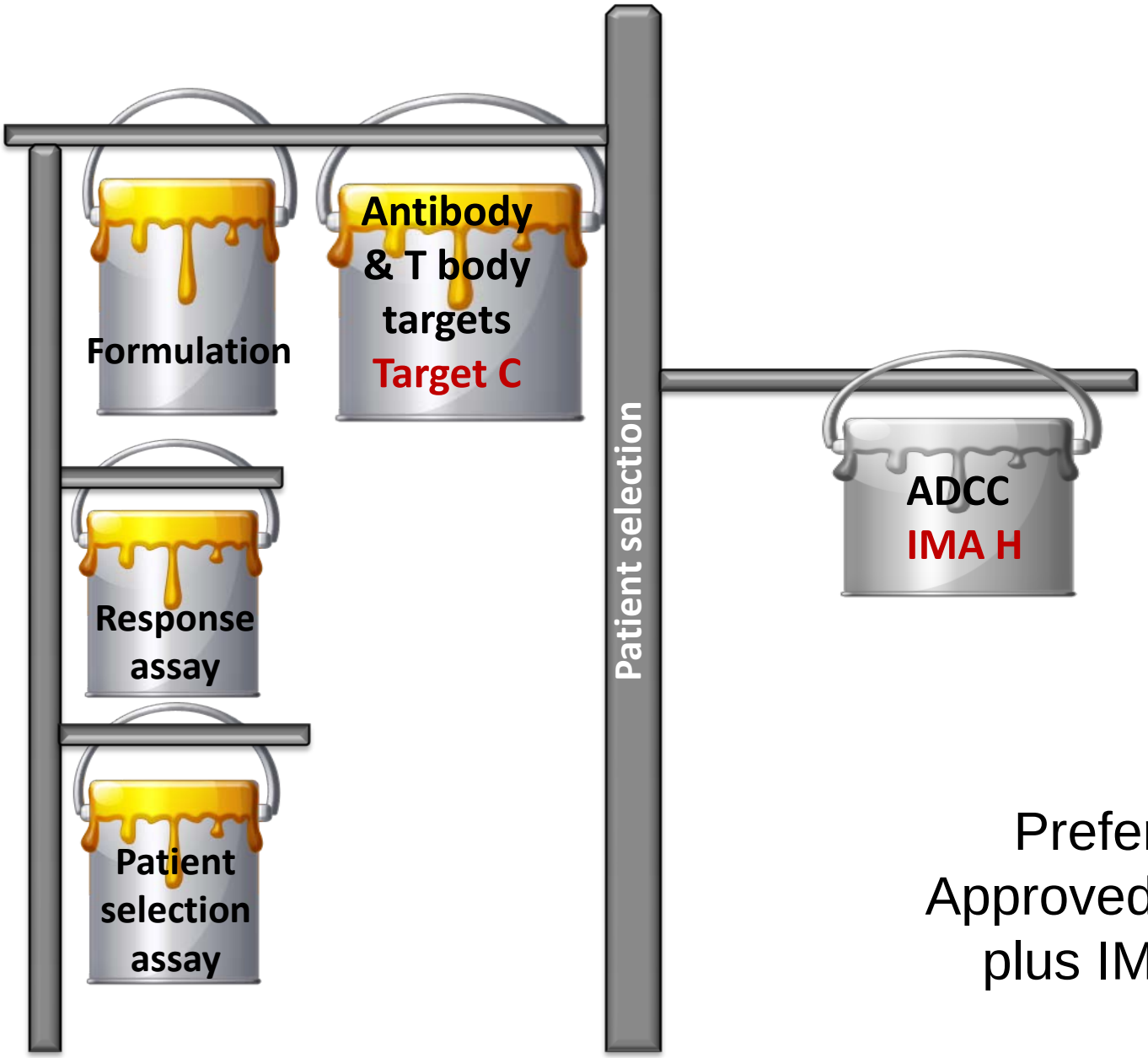
Prefer recombinant T cell receptor
Plus vaccine to maintain
T cell survival post therapy

Working Group Prioritized Targets & Agents

- A: Vaccine Targets
  - HER2, HPV E6/7, MUC1, MAGE A3, WT1, NY-ESO-1, PSA
- **B: T-Cell Therapy Targets:**
  - **HER2, HPV E6/7, MUC1, MAGE A3, WT1, NY-ESO-1, PSA**
- C: Antibody & T Body Targets
  - HER2, EGFR, CD20, CD19

- D: IMA: Vaccine adjuvants, dendritic cell activators, T cell attracting chemokines, or DC growth factors
  - CpG, CD40, IL-12
- **E: IMA: T cell stimulators or T cell growth factors**
  - **IL7, IL21, IL15, Anti-4-1BB**
- **F: IMA: Inhibitors of T cell checkpoint blockade**
  - **Anti-CTLA-4, Anti-PD1**
- G: IMA: Agents to neutralize or inhibit suppressive cells, cytokines, and enzymes
  - Anti-TGF beta, IDO inhibitors, Anti-IL10
- IMA H: Agents to increase antibody dependent cellular cytotoxicity (ADCC)
  - IL7, CpG, Anti-CD40, IL12, Anti-4-1BB or chimeric antibody receptors (CAR)

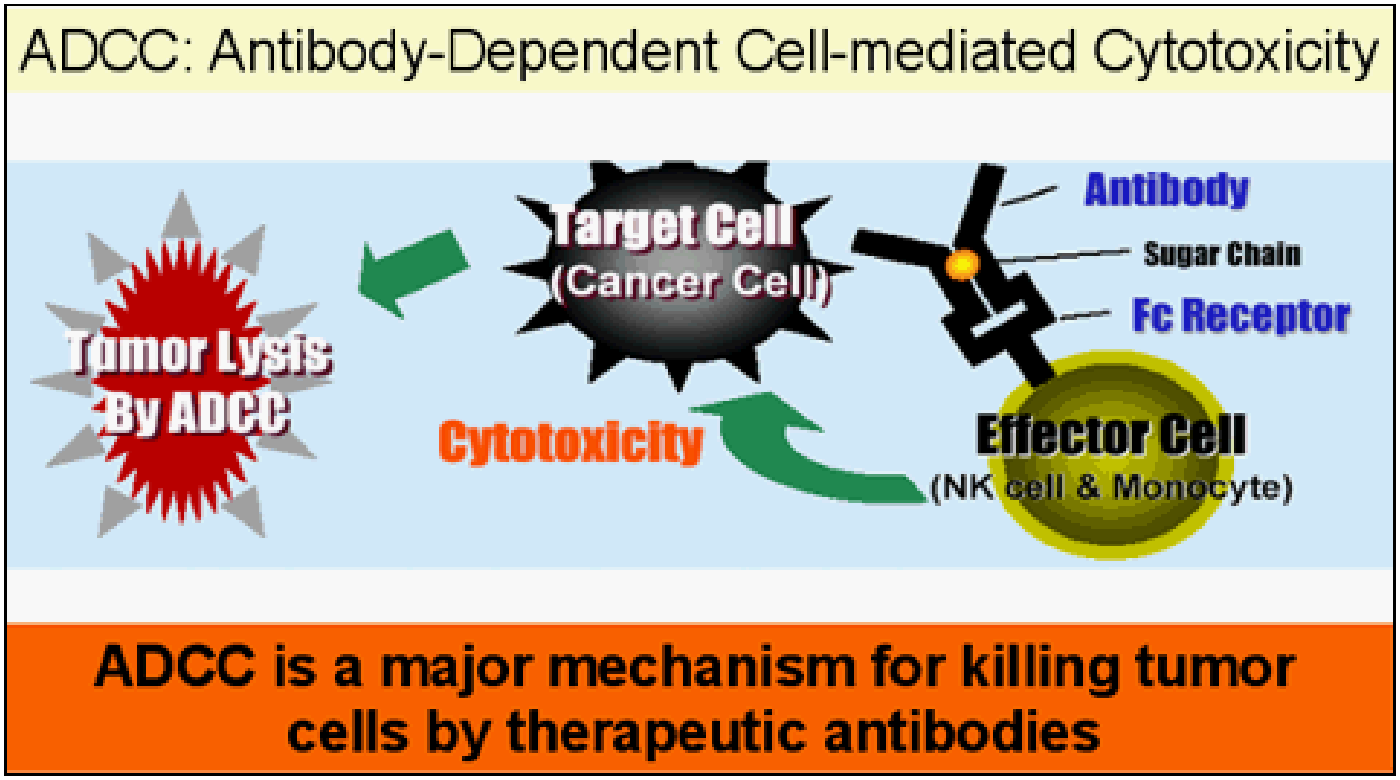
ANTIBODY SCAFFOLD



Prefer
Approved Ab
plus IMA

Six Approved Antibodies Mediate Effects, in part, through Antibody Dependent Cellular Cytotoxicity (ADCC)

- Ab binds to cancer cell
- Fc portion of Ab binds to Fc Receptor on WBC
- WBC apposed to cancer cells kill cancer cells
- Degree of killing depends on level of binding.



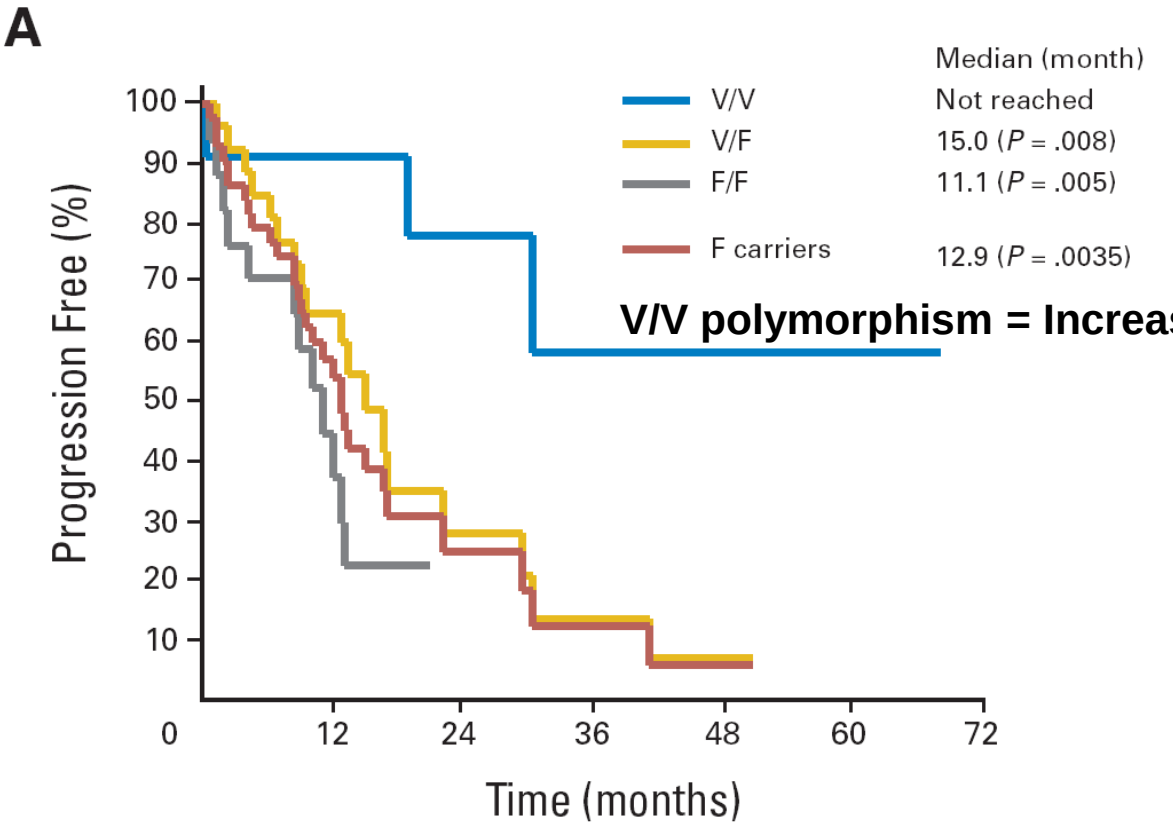
Antibody Target

- At least 3 commonly used FDA approved antibodies require, in part, host participation, i.e. antibody dependent cellular cytotoxicity (ADCC) for optimal therapy
  - Rituximab (anti-CD20)
  - Cetuximab (anti-EGFR)
  - Trastuzumab (anti-HER2/neu)

ADCC is an Important Mechanism for Herceptin Function:

Progression free survival depends on level of binding of Fc portion to Fc receptors on NK cells

Background: FcR valine (V/V) polymorphism is more effective than phenylalanine (F) in mediating ADCC



V/V polymorphism = Increased FcRγ III binding

Musolino, A. et al. J Clin Oncol; 26:1789-1796 2008

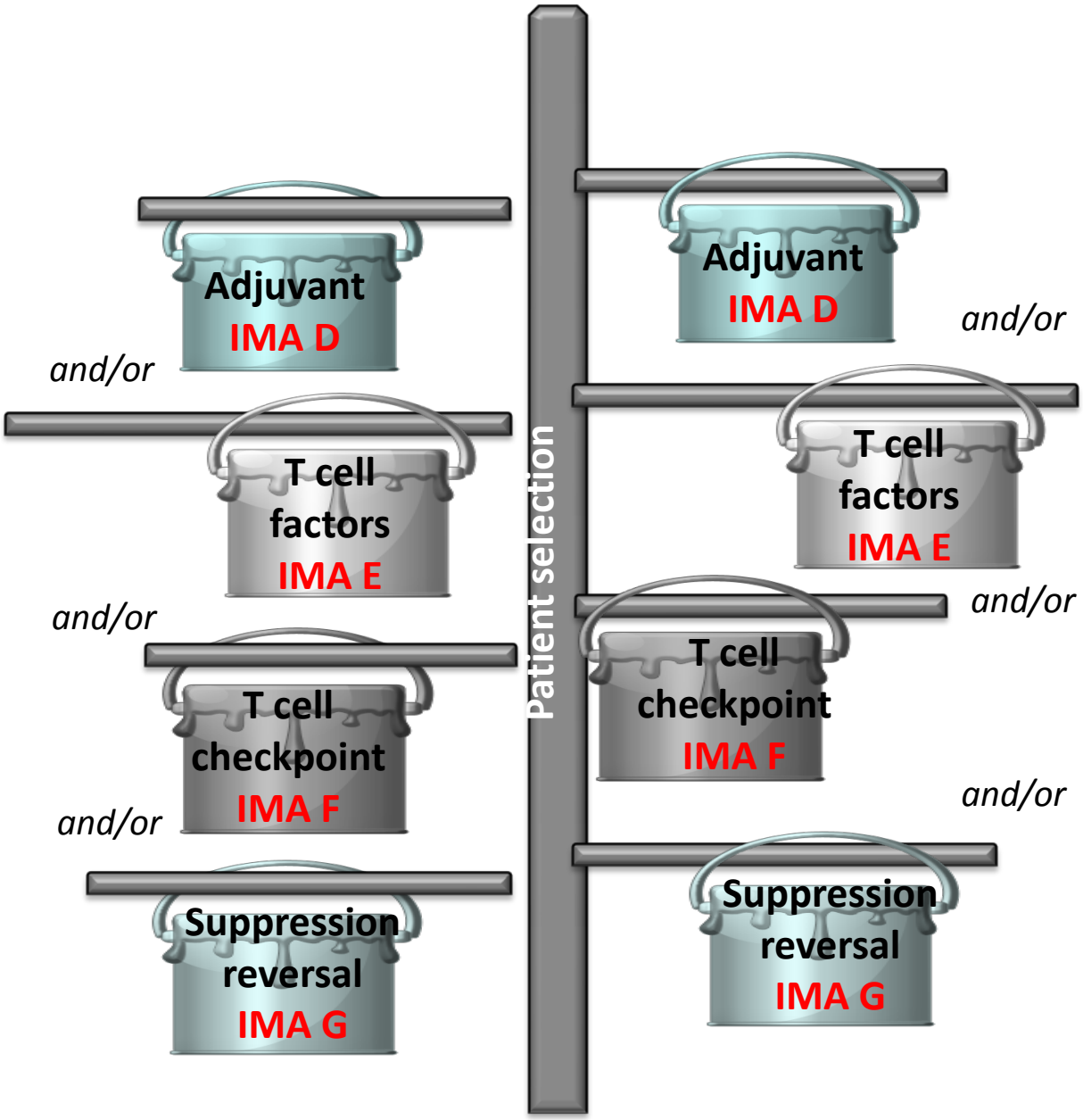
JOURNAL OF CLINICAL ONCOLOGY

Working Group Prioritized Targets & Agents

- A: Vaccine Targets
  - HER2, HPV E6/7, MUC1, MAGE A3, WT1, NY-ESO-1, PSA
- B: T-Cell Therapy Targets:
  - HER2, HPV E6/7, MUC1, MAGE A3, WT1, NY-ESO-1, PSA
- **C: Antibody & T Body Targets**
  - **HER2, EGFR, CD20, CD19**

- D: IMA: Vaccine adjuvants, dendritic cell activators, T cell attracting chemokines, or DC growth factors
  - **CpG, CD40, IL-12**
- E: IMA: T cell stimulators or T cell growth factors
  - **IL7**, IL21, IL15, **Anti-4-1BB**
- F: IMA: Inhibitors of T cell checkpoint blockade
  - anti-CTLA-4, Anti-PD1
- G: IMA: Agents to neutralize or inhibit suppressive cells, cytokines, and enzymes
  - Anti-TGF beta, IDO inhibitors, anti-IL10
- **IMA H: Agents to increase antibody dependent cellular cytotoxicity (ADCC)**
  - **IL7, CpG, Anti-CD40, IL12, Anti-4-1BB or chimeric antibody receptors (CAR)**

IMMUNE MODIFIER AGENT SCAFFOLD



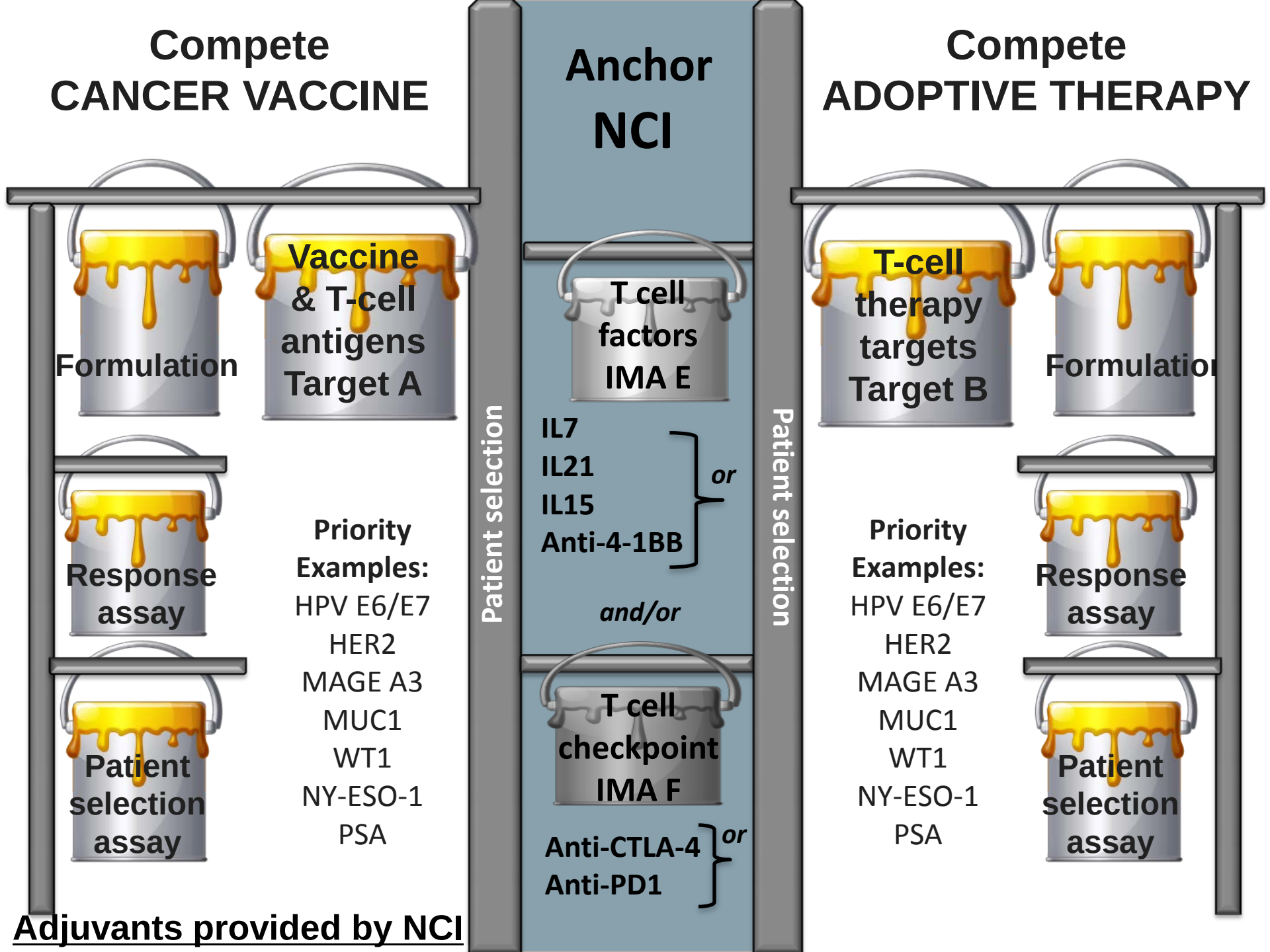
Rational Sequence

(1) IMA to activate autochthonous T cell responses

(2) IMA to expand & maintain T cell response

RECOMMENDATION

- Four STRAPs representing three scaffolds
  - Vaccine: Viral antigen
  - Vaccine: Self cancer antigen
  - Adoptive Cellular therapy
  - Antibody therapy
- NCI “anchor” at least one of two buckets
  - E: IMA: T cell stimulators or T cell growth factors
    - IL7, IL21, IL15, Anti-4-1BB
  - F: IMA: Inhibitors of T cell checkpoint blockade
    - Anti-CTLA-4, Anti-PD1
- NCI provide adjuvant
  - From Immunotherapy Agents Workshop
- Call for applications for Targets side of scaffold


Compete
CANCER VACCINE
Anchor
NCI
Compete
ADOPTIVE THERAPY
Formulation
Vaccine
& T-cell
antigens
Target A
Response
assay
Patient
selection
assay
Priority
Examples:
HPV E6/E7
HER2
MAGE A3
MUC1
WT1
NY-ESO-1
PSA
Patient selection
T cell
factors
IMA E
IL7
IL21
IL15
Anti-4-1BB
or
and/or
T cell
checkpoint
IMA F
Anti-CTLA-4
Anti-PD1
or
Patient selection
T-cell
therapy
targets
Target B
Formulation
Response
assay
Patient
selection
assay
Priority
Examples:
HPV E6/E7
HER2
MAGE A3
MUC1
WT1
NY-ESO-1
PSA
Adjuvants provided by NCI

Why is this approach to investigator-driven translational research necessary?

Submitted Translational Research Opportunity:

HPV 16/18 E6/E7 DNA prime: Vaccinia boost (CIN3)

[Goal: Develop effective therapy that can be tested and used at multiple institutions

- Deconstruction and restructure
  - DNA prime
  - Provide adjuvants for DNA prime (not commonly available)
    - **CpG or CD40,**
  - Boost with recombinant vaccinia
    - Effective, but repeated vaccination limited due to vaccinia specific immunity
  - Provide adjuvants for DNA boosting to allow repeated vaccination
    - **CpG or CD40,**
  - Provide IMA to augment & sustain response
    - T cell growth factor (**IL7**) or
    - T cell stimulator (**Anti- 4-1BB)**

Submitted Translational Research Opportunity:
MART-1, gp100, MAGE-A3, tyrosinase peptides: Dendritic cells as adjuvants

Goal: Develop effective therapy that can be tested and used at multiple institutions

- Deconstruction and restructure
  - MAGE-A3 only (priority antigen)
  - Provide alternative formulation (non-DC)
    - Provide adjuvants for alternative formulation
    - **CpG** or **IL-12**
  - Provide IMA to augment & sustain response
    - T cell growth factors
      - **IL15**
    - Inhibitors of T cell checkpoint blockade
      - **Anti-CTLA-4**
    - Agents to neutralize or inhibit suppressive cells, cytokines, and enzymes
      - **Anti-TGF beta**

Submitted Translational Research Opportunity:
TIL therapy of melanoma with myelosuppressive conditioning + IL2
Goal: Develop effective therapy that can be tested and used at multiple institutions

- Deconstruction and restructure
  - **Vaccine** prior to in vitro T cell growth
    - **Or, Recombinant TCR**
  - Target with restricted distribution vs. TIL
    - T-Cell Therapy Targets:
      - **NY-ESO-1**
    - T-Body Targets
      - **CD19**
  - T cell growth factors post transfer
    - **IL7, IL15 or IL21**
  - **Vaccine post transfer**

Submitted Translational Research Opportunity:
Therapy with antibody to GD2 with IL2
Goal: Develop effective therapy that can be tested and used at multiple institutions

- Deconstruction and restructure
  - Commercial antibody known to function in part via antibody dependent cellular cytotoxicity (ADCC)
  - Supply agents known to increase ADCC for iterative early phase trials
    - **IL7, CpG, Anti-CD40, IL12, Anti-4-1BB**
  - Move best results into randomized Phase III with cooperative groups

The Translational Research Acceleration Initiative

Clinical Trials and Translational Research Advisory Committee

November 4, 2009

Lynn M. Matrisian

Special Assistant, NCI

IRM Pilot Prioritization Project

Translational Science Meetings | **Request for Information** | **NCI-directed Workshops**

Translational Research Opportunities

IRM Prioritization Working Group: (Extramural & intramural content experts)

113 Opportunities
174 key component candidates

Scientific Prioritization

Clinical Trials and Translational Research Advisory Committee (Extramural) Nov 4, 2009

Limited # scaffolds with prioritized candidates in buckets

Recommended priority scaffolds and buckets

IRM Pilot Prioritization Project: NEXT STEPS

Scientific Prioritization

Recommended scaffolds and buckets

NCI Prioritization:

- **Logistical feasibility**
- **Clinical Need**
- **Appropriateness for NCI investment**

- **Select candidate(s) from IMA bucket(s) as anchor**
- **Select Target bucket(s) for competition**

Complete by December 2009

IRM Pilot Prioritization Project

Top IMA candidate(s) and top target bucket(s)
Develop 1-4 IRM
Special Translational Research
Acceleration Project (STRAP) concepts

↓

NCI Leadership

↓

Advisory boards
as appropriate

Request(s) for Supplements/Proposals/ Applications

Process to Accelerate Translational Science Initiative

Gather information

Prioritize

Fund & Manage

Special Translational Research Acceleration Projects (**STRAPs**)

- Requirements:
  - Goal of completing early stage human studies
  - Project management plan
  - Specific development milestones and timelines
  - Development/commercialization strategy
- Funds for new and/or expanded projects
- Project management would link new or existing teams and projects and facilitate hand-offs between groups
- Opportunities to include industry/foundation funding or participation

IRM STRAP

Call for Supplements/Applications/Proposals for 1-4 IRM STRAPS

Supplements/ existing mechanisms:

- NeXT
- R01
- P01
- Cooperative Groups
- NCI clinical center
- RAPID
- EDRN
- SPOREs
- Cancer Centers
- etc

Scientific/Feasibility Review using Criteria set for remaining IRM components:

- Formulation
- Combination
- Assay for response
- Assay to select pts
- Availability pts for clinical trials

New (if necessary):

- RFAs
- RFPs
- Cooperative Agreements
- CRADAs
- etc

NCI leadership

Advisory board as appropriate

Funded STRAP

FY2010

Staging of Process to Accelerate Translational Science (PATS) Subgroups

Determine pathway-specific criteria

Pilot Projects for each of the Pathways

Fall 2009

Immune Response Modifier

Therapeutic intent:
In conjunction with NCI Experimental Therapeutics Program

Agents

Winter 2009/2010

Biospecimens

Lifestyle Alterations

Spring 2010

Imaging

Interventive Devices

Staging of Process to Accelerate Translational Science (PATS) Subgroups

Determine pathway-specific criteria

Pilot Projects for each of the Pathways

Fall 2009

Immune Response Modifier

Therapeutic intent:
In conjunction with NCI Experimental Therapeutics Program

Agents

Winter 2009/2010

Biospecimens

Lifestyle Alterations

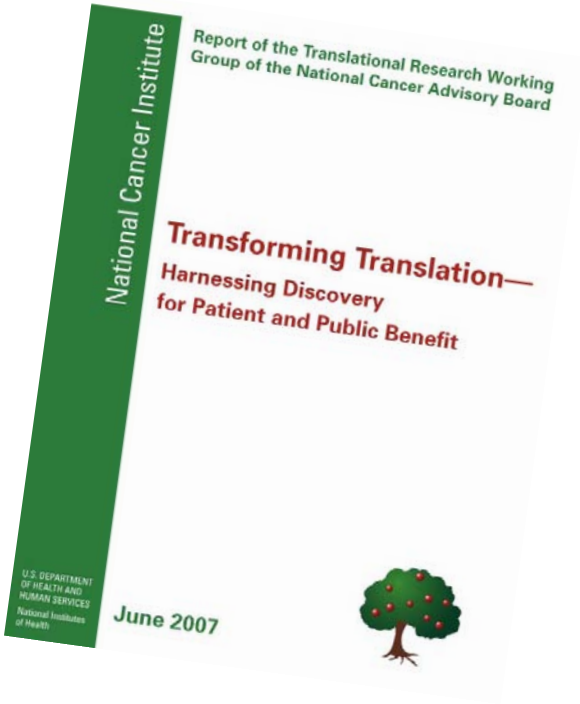
Spring 2010

Imaging

Interventive Devices

Consistent with TRWG underlying principles

- Evaluate the status of NCI's investment in translational research & envision its future in an inclusive, representative & transparent manner
- Overcome barriers resulting from the dispersal of translational research throughout the NCI DOC's
- Change: "business as usual" is untenable
- Will it accelerate translational cancer research? Evaluation in planning stage



IRMP WG Report: RECOMMENDATIONS

- Four STRAPs representing three scaffolds
  - Vaccine: Viral antigen
  - Vaccine: Self cancer antigen
  - Adoptive Cellular therapy
  - Antibody therapy
- NCI “anchor” at least one of two buckets
  - E: IMA: T cell stimulators or T cell growth factors
    - IL7, IL21, IL15, Anti-4-1BB
  - F: IMA: Inhibitors of T cell checkpoint blockade
    - anti-CTLA-4, Anti-PD1
- NCI provide adjuvant
  - From Immunotherapy Agents Workshop
- Call for applications for Targets side of scaffold

IRMP WG Report: RECOMMENDATIONS

- Target antigens in buckets represent high priority examples
  - HPV E6/E7, HER2, MAGE A3, MUC1, WT1, NY-ESO-1, PSA
- Applications are not restricted to these targets
- Submitted targets must demonstrate equivalency to priority candidates in scientific validity and feasibility

IRMP WG Report: RECOMMENDATIONS

- Applications address remaining critical components of scaffold
  - Formulation
  - Assay for immune response
  - Assay to select patient population
  - Availability of patients for clinical trials
- Are reviewed using pre-determined and pre-weighted criteria and subcriteria
  - All of above
  - Combination regimen

IRMP WG Report: RECOMMENDATIONS

- NCI makes choice of IMA anchors based on logistical feasibility
- NCI decisions on reviewed applications take into account:
  - Clinical need
    - Rare diseases
    - Immunoprevention
  - Appropriateness for NCI investment
    - Redundancy with industry

IRMP WG Report: RECOMMENDATIONS

- Immune Response Modifier Special Translational Research Acceleration Projects be launched, reviewed, and funded in FY2010

IRMP WG Report

- DISCUSSION

- Does CTAC accept the IRMP WG report and recommendations?